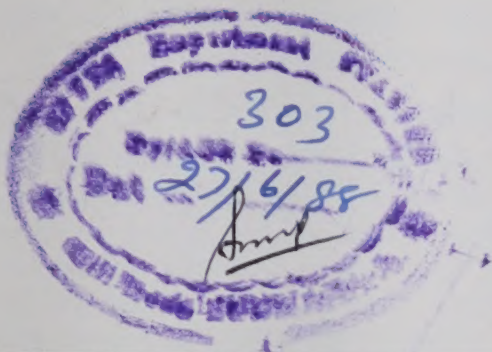


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SECTION B  
(Organic including Medicinal)



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## Model Studies for an Asymmetric Synthesis of (+)-4-Demethoxydaunomycinone†

A R MEHENDALE\*, ALPANA KULKARNI & GEETA NAGARAJAN

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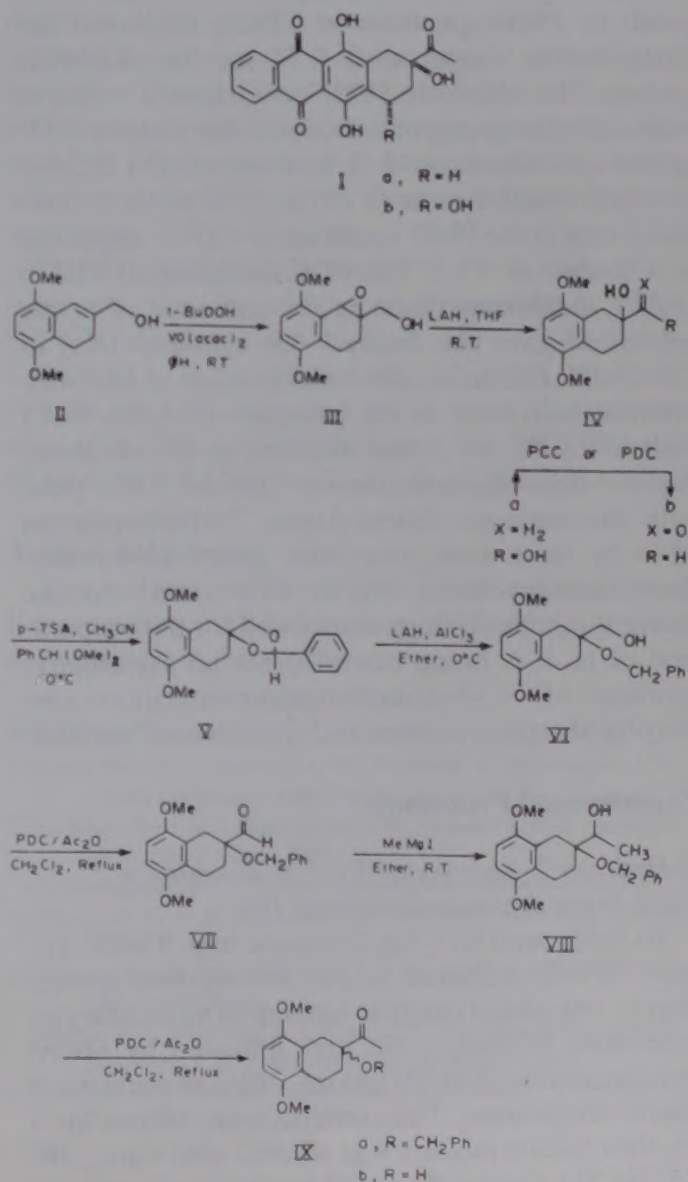
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2-Hydroxymethyl-5,8-dimethoxy-3,4-dihydronaphthalene (II) on *t*-butyl hydroperoxide oxidation followed by LAH reduction gives 2-hydroxy-2-hydroxymethyl-5,8-dimethoxy-1,2,3,4-tetrahydronaphthalene (IVa) in 85% yield. The corresponding O-benzyl derivative (VI) on PDC oxidation affords 2-benzyloxy-5,8-dimethoxy-1,2,3,4-tetrahydronaphthyl-2-aldehyde (VII), which on Grignard reaction with methylmagnesium iodide followed by PDC oxidation affords the desired (±)-2-acetyl-2-O-benzyl-5,8-dimethoxy-1,2,3,4-tetrahydronaphthalene (IXa) in 70% yield. Friedel-Crafts condensation of IXa with phthalic anhydride in the presence of AlCl<sub>3</sub>-NaCl melt furnishes (±)-4-demethoxy-7-deoxydaunomycinone (Ia) in 74% yield, which on 7-hydroxylation affords the desired (±)-4-demethoxydaunomycinone (Ib) in 40% yield.

In a previous paper from our laboratory, Rama Rao and coworkers<sup>1</sup> reported a stereo-convergent synthesis of (+)-4-demethoxydaunomycinone (Ib) in 40% yield. Although the strategy<sup>1</sup> was attractive, it was relatively less useful for large scale preparation of Ib, because as much as half the starting material had to be epimerised and recycled. From this point of view, there was a need to employ a key intermediate such as 2-hydroxymethyl-5,8-dimethoxy-3,4-dihydronaphthalene (II), which was devoid of any chiral centre, so that in the absence of any kinetic resolution, II would quantitatively give the desired optically active *R*-(-)-2-acetyl-2-hydroxy-5,8-dimethoxy-1,2,3,4-tetrahydronaphthalene (IXb) after a suitable sequence of reactions. In order to assess the feasibility of the scheme, it was first decided to synthesise racemic IXb and then to extend the same for its asymmetric synthesis.

The requisite AB synthon IXb was prepared as its benzyl ether (IXa) in seven steps starting from II<sup>2</sup> (Scheme 1).

Non-asymmetric Sharpless epoxidation<sup>3</sup> of the allylic alcohol (II) using *t*-butyl hydroperoxide (TBHP) in the presence of vanadylacetylacetonate [VO(acac)<sub>2</sub>] in benzene at 25°C gave an unstable epoxide (III) in 90% yield. It was immediately reduced with LAH in THF at 25° to obtain hydroxy-2-hydroxymethyl-5,8-dimethoxy-1,2,3,4-tetrahydronaphthalene (IVa) in 83% yield after crystallisation from benzene. The formation of the diol (IVa) was evident from its PMR spectrum in CDCl<sub>3</sub> which showed the absence of the signal at δ 4.25 due to H-1 proton of the epoxide. Attempts to



SCHEME 1

†NCL Communication No. 4291.

oxidise the primary alcoholic group in IVa to an aldehydic group employing usual oxidising agents such as PCC or PDC led only to the formation of the undesired 5,8-dimethoxy-2-tetralone as the major product with elimination of hydroxymethyl group, and only trace amount of the desired aldehyde (IVb) was obtained. The difficulty was circumvented by protecting the hydroxyl groups of IVa with  $\alpha,\alpha$ -dimethoxytoluene to obtain V in 70% yield which on hydrogenolysis with LAH- $\text{AlCl}_3$  in ether at  $0^\circ\text{C}$  gave 2-O-benzyl-5,8-dimethoxy-2-hydroxymethyl-1,2,3,4-tetrahydronaphthalene (VI) in 86% yield. The evidence for the presence of the benzyl group on tertiary hydroxyl group was provided by its PMR spectrum in  $\text{DMSO}-d_6$  which exhibited a one-proton triplet at  $\delta$  4.74 (exchangeable with  $\text{D}_2\text{O}$ ) due to primary OH. PDC oxidation of VI in boiling dichloromethane in the presence of acetic anhydride afforded 2-O-benzyl-5,8-dimethoxy-1,2,3,4-tetrahydronaphthalene-2-aldehyde (VII) in 67% yield. Its PMR spectrum in  $\text{CDCl}_3$  displayed the characteristic singlet at  $\delta$  9.72 for the aldehydic proton. The aldehyde (VII) on Grignard reaction with methylmagnesium iodide in ether yielded 2-O-benzyl-5,8-dimethoxy-2-(1-hydroxyethyl)-1,2,3,4-tetrahydronaphthalene (VIII) in 82% yield. Its methyl group in the PMR spectrum in  $\text{CDCl}_3$  appeared as a doublet at  $\delta$  1.2. The PDC oxidation of VIII in boiling dichloromethane in the presence of acetic anhydride gave the desired AB synthon (IXa) in 70% yield. Friedel-Crafts condensation of IXa with phthalic anhydride in the presence of  $\text{AlCl}_3$ -NaCl melt at  $180^\circ\text{C}$  for 5 min resulted in ( $\pm$ )-4-demethoxy-7-deoxydaunomycinone (Ia) in 74% yield with simultaneous debenzylation. 7-Hydroxylation of Ia by the known procedure gave ( $\pm$ )-4-demethoxydaunomycinone (Ib) in 40% yield<sup>4</sup>. As the above synthetic strategy works well for the preparation of Ia, it is being extended for an asymmetric synthesis of (+)-4-demethoxydaunomycinone employing Sharpless asymmetric epoxidation<sup>5</sup> method.

## Experimental Procedure

### 2-Hydroxy-2-hydroxymethyl-5,8-dimethoxy-1,2,3,4-tetrahydronaphthalene (IV)

To compound II (5.5 g, 25 mmol, m.p.  $93-95^\circ$ , lit.<sup>2</sup> m.p.  $93-95^\circ$ , prepared as per the reported procedure<sup>2</sup>), was added catalytic amount of vanadylacetylacetonate  $\text{VO}(\text{acac})_2$  (60 mg), followed by *t*-butyl hydroperoxide (TBHP) (30 ml, 70%) in portions at room temperature. The contents were stirred for 4 hr, the reaction mixture was washed with water, dried ( $\text{Na}_2\text{SO}_4$ ) and evaporated to obtain the epoxide III as a gummy product (5.35 g, 90%); PMR

( $\text{CDCl}_3$ ):  $\delta$  4.26 (s, 1H, epoxide H). It was immediately subjected to LAH reduction.

To a solution of III (5.35 g, 22.7 mmol) in dry THF (30 ml), LAH (0.863 g, 22.7 mmol) was added in portions during 10 min at room temperature and further stirred at the same temperature for 4 hr. Reaction mixture was worked up by addition of saturated aq sodium carbonate and the white solid obtained was filtered and washed with chloroform. The filtrate on drying ( $\text{Na}_2\text{SO}_4$ ) and evaporation gave a semi-solid, which on crystallisation from benzene gave IVa as colourless needles (4.5 g, 83%), m.p.  $130-132^\circ$ ; IR (nujol): 3500 (OH),  $1600\text{ cm}^{-1}$  (aromatic); PMR ( $\text{CDCl}_3$ ):  $\delta$  1.53-2.30 (m, 3H, Ha-3, Hb-3 and OH), 2.41-2.91 (m, 4H, benzylic), 3.6 (bs, 3H,  $\text{CH}_2\text{OH}$  & OH), 3.84 (s, 6H,  $2 \times \text{OCH}_3$ ), 6.73 (s, 2H, aromatic); MS:  $m/z$  238  $\text{M}^+$  (Found: C, 65.3; H, 7.3.  $\text{C}_{13}\text{H}_{18}\text{O}_4$  requires C, 65.5; H, 7.6%).

### Benzylidene derivative (V)

To the diol IVa (2 g, 8.4 mmol) in acetonitrile (10 ml),  $\alpha,\alpha$ -dimethoxytoluene (1.15 g, 7.76 mmol) and catalytic amount of *p*-toluenesulphonic acid (50 mg) were added at  $0^\circ\text{C}$ . The reaction mixture was slowly brought to room temperature. While stirring for 30 min, all the starting material disappeared (TLC). Powdered sodium bicarbonate was added, the reaction mixture stirred for 30 min at  $0^\circ\text{C}$ , allowed to settle and supernatant acetonitrile decanted. The inorganic salts were washed with chloroform and both the organic layers were mixed, washed with water, dried ( $\text{Na}_2\text{SO}_4$ ) and solvent removed under reduced pressure to afford V as a semi-solid (1.9 g, 69%). It crystallised from ether - pet. ether mixture m.p.  $95-98^\circ$ ; IR (nujol)  $1600\text{ cm}^{-1}$  (aromatic); PMR ( $\text{CDCl}_3$ ):  $\delta$  1.76-2.13 (m, 2H, Ha-3, Hb-3), 2.85 (bs, 4H, benzylic), 4.74 (s, 8H,  $20\text{CH}_3$  and  $-\text{CH}_2\text{O}-$ ), 5.93 and 6.0 (s, 1H, isomeric benzylidene proton), 6.54 (s, 2H, aromatic), 7.23-7.54 (m, 5H, aromatic); MS:  $m/z$  326 ( $\text{M}^+$ ) (Found: C, 73.8; H, 6.8.  $\text{C}_{20}\text{H}_{22}\text{O}_4$  requires C, 73.6; H, 6.7%).

### 2-O-Benzyl-2-hydroxymethyl-5,8-dimethoxy-1,2,3,4-tetrahydronaphthalene (VI)

Anhydrous aluminium chloride (1.6 g, 12 mmol) was dissolved in dry ether (20 ml) at  $0^\circ\text{C}$  and LAH (0.115 g, 3 mmol) added to it and stirred at  $0^\circ\text{C}$  for 1 hr to form a homogeneous mixture. To this V in ether (20 ml) was added during 10 min, maintaining the temperature above  $5^\circ$ . After complete addition, the reaction mixture was further stirred for 1 hr at  $5^\circ\text{C}$  till there was no starting material (TLC). The complex was decomposed by addition of ethyl acetate and dil. HCl. The reaction mixture was extensively extracted with chloroform, the organic layer washed with brine, dried ( $\text{Na}_2\text{SO}_4$ ) and evaporated

to give VI as a colourless solid which crystallised from carbon tetrachloride (1.7 g, 86%), m.p. 96-98°; IR (nujol): 3480 (OH) and 1600  $\text{cm}^{-1}$  (aromatic); PMR ( $\text{CDCl}_3$ ):  $\delta$  1.88-2.06 (*m*, 2H, Ha-3, Hb-3), 2.64-2.94 (*m*, 4H, benzylic), 3.63 (*s*, 2H,  $\text{CH}_2\text{OH}$ ), 3.87 (*s*, 6H,  $2 \times \text{OCH}_3$ ), 4.56 (*s*, 2H,  $\text{OCH}_2\text{Ph}$ ), 6.62 (*s*, 2H, aromatic), 7.23-7.36 (*m*, 5H, aromatic); PMR ( $\text{DMSO}-d_6$ ):  $\delta$  4.74 (*t*, 1H, OH, vanishes after  $\text{D}_2\text{O}$  exchange); MS:  $m/z$  328 ( $\text{M}^+$ ) (Found: C, 73.0; H, 7.2.  $\text{C}_{20}\text{H}_{24}\text{O}_4$  requires C, 73.1; H, 7.3%).

#### 2-O-Benzyl-5,8-dimethoxy-

#### 1,2,3,4-tetrahydronaphthalene-2-aldehyde (VII)

To a stirred solution of pyridinium dichromate (PDC) (0.361 g, 0.96 mmol) in dichloromethane (5 ml), acetic anhydride (0.49 g, 4.8 mmol) and alcohol (VI, 0.525 g, 1.6 mmol) were rapidly added at room temperature. After refluxing for 2 hr, the reaction mixture was cooled and diluted with ether (30 ml). The solvent was decanted and the residue washed thoroughly with ether. The combined organic phase was concentrated and filtered through silica gel to give VII (0.35 g, 67.1%) as a semi-solid; IR (nujol): 1720  $\text{cm}^{-1}$  ( $\text{C}=\text{O}$ ); PMR ( $\text{CDCl}_3$ ):  $\delta$  2.0 (*t*,  $J=8\text{Hz}$ , 2H, Ha-3, Hb-3), 2.64-3.0 (*m*, 4H, benzylic), 3.74 (*s*, 6H,  $2 \times \text{OCH}_3$ ), 4.5 (*s*, 2H,  $-\text{OCH}_2\text{Ph}$ ), 6.58 (*s*, 2H, aromatic), 7.23-7.32 (*m*, 5H, aromatic), 9.72 (*s*, 1H, CHO).

#### 2-O-Benzyl-5,8-dimethoxy-2-(1-hydroxyethyl)-1,2,3,4-tetrahydronaphthalene (VIII)

To a solution of methylmagnesium iodide (0.166 g, 1 mmol) in dry ether (5 ml) was added dropwise a solution of VII (0.326 g, 1 mmol) in dry ether (5 ml) at room temperature under  $\text{N}_2$  atmosphere. The reaction mixture was further stirred for 1 hr, poured into a cooled saturated aq ammonium chloride and was repeatedly extracted with ether ( $3 \times 20\text{ ml}$ ). The combined organic layer was washed with water, dried ( $\text{Na}_2\text{SO}_4$ ) and evaporated under reduced pressure to yield VIII as a semi-solid, (0.290 g, 85%); IR ( $\text{CHCl}_3$ ): 3400  $\text{cm}^{-1}$  (OH); PMR ( $\text{CDCl}_3$ ):  $\delta$  1.2 (*d*,  $J=6\text{Hz}$ , 3H,  $\text{CH}_3$ ), 2.12 (*d*, 2H,  $J=10\text{Hz}$ , Ha-3, Hb-3), 2.48-2.92 (*m*, 4H, benzylic), 3.72 (*s*, 6H,  $2 \times \text{OCH}_3$ ), 3.98 [*q*,  $J=6\text{Hz}$ , 1H,  $\text{CH}(\text{OH})\text{CH}_3$ ], 4.41 (*ABq*,  $J=7.5\text{ Hz}$ , 2H,  $\text{OCH}_2\text{Ph}$ ), 6.66 (*s*, 2H, aromatic), 7.24 (*s*, 5H, aromatic); MS:  $m/z$  342 ( $\text{M}^+$ ).

#### 2-Acetyl-2-O-benzyl-5,8-dimethoxy-1,2,3,4-tetrahydronaphthalene (IXa)

To a stirred solution of pyridinium dichromate (PDC) (0.176 g, 0.47 mmol) in dichloromethane (4 ml) acetic anhydride (0.24 g, 2.35 mmol) and the secondary alcohol VIII (0.27 g, 0.78 mmol) were rapidly added at room temperature. After refluxing

for 2 hr, the reaction mixture was cooled, diluted with ether (20 ml), the solvent decanted and the residue washed thoroughly with ether. The combined organic phase was filtered through silica gel to give IXa as a colourless solid which recrystallised from pet. ether (0.19 g, 71%), m.p. 106-8°; IR (nujol): 1720  $\text{cm}^{-1}$  ( $\text{C}=\text{O}$ ); PMR ( $\text{CDCl}_3$ ):  $\delta$  1.77-2.08 (*m*, 2H, Ha-3, Hb-3), 2.24 (*s*, 3H,  $\text{COCH}_3$ ), 2.57-3.0 (*m*, 4H, benzylic), 3.74 (*s*, 6H,  $2 \times \text{OCH}_3$ ), 4.33 (*ABq*,  $J=11\text{Hz}$ , 2H,  $\text{OCH}_2\text{Ph}$ ), 6.55 (*s*, 2H, aromatic), 7.00 (*s*, 5H, aromatic); MS:  $m/z$  340 ( $\text{M}^+$ ) (Found: C, 74.3; H, 7.1.  $\text{C}_{21}\text{H}_{24}\text{O}_4$  requires C, 74.1; H, 7.1%).

#### 4-Demethoxy-7-deoxydaunomycinone (Ia)

A mixture of anhydrous aluminium chloride (0.707 g, 5.3 mmol) and sodium chloride (0.288 g, 4.93 mmol) was heated at 180°C to form a uniform melt. To this was added a mixture of phthalic anhydride (0.313 g, 2.12 mmol), IXa (0.18 g, 0.53 mmol) and the resulting mixture was stirred at 180-90°C for 5 min. After cooling, the reaction mixture was digested with saturated oxalic acid solution on a water bath for 1 hr, cooled and extracted with chloroform ( $4 \times 10\text{ ml}$ ). The chloroform layer was successively washed with 5% aq sodium bicarbonate, brine, dried and evaporated to give Ia as orange-red solid, which recrystallised from hexane-benzene as red needles (0.137 g, 75%), m.p. 216-17° (lit.<sup>6</sup> m.p. 210-12°); IR (nujol): 3460 (OH), 1710 ( $\text{C}=\text{O}$ ), 1655 (quinone  $\text{C}=\text{O}$ ), 1580  $\text{cm}^{-1}$  (aromatic); PMR ( $\text{CDCl}_3$ ):  $\delta$  1.5-1.9 (*m*, 2H, Ha-b, Hb-8), 2.46 (*s*, 3H,  $\text{COCH}_3$ ), 3.12 (*bs*, 4H, benzylic), 3.72 (*bs*, 1H, OH), 7.6-7.8 (*m*, 2H, aromatic), 8.2-8.4 (*m*, 2H, aromatic), 13.5 (*s*, 2H,  $2 \times \text{OH}$ ); MS:  $m/z$  352 ( $\text{M}^+$ ) (Found: C, 68.4; H, 4.8. Calc. for  $\text{C}_{20}\text{H}_{16}\text{O}_6$ : C, 68.2; H, 4.6%).

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# Syntheses of (±)-Deoxyschizandrin & the Lignan, 1,4-Bis(3,4-dimethoxyphenyl)-2,3-dimethylbutane

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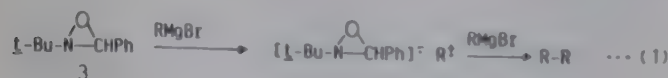
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(±)-Deoxyschizandrin (**1**) has been synthesised through a dimerisation reaction as a key step. The Grignard reagent from 1-(3, 4, 5-trimethoxyphenyl)-2-bromopropane (**10**) on reaction with 2-*t*-butyl-3-phenyloxaziridine gives 1,4-bis(3, 4, 5-trimethoxyphenyl)-2, 3-dimethylbutane (**11**), which is cyclised using vanadium oxytrifluoride to get deoxyschizandrin (**1**). Following the above methodology, 1,4-bis(3,4-dimethoxyphenyl)-2, 3-dimethylbutane (**2**), a lignan has also been prepared.

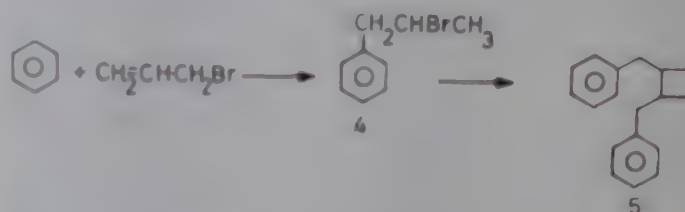
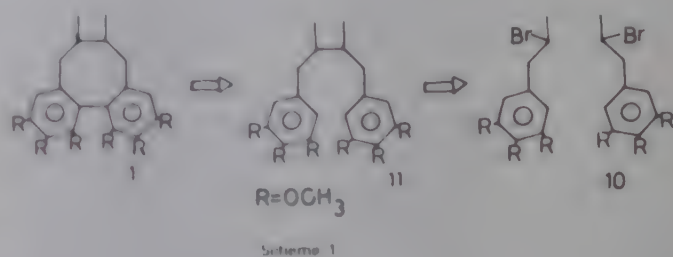
(±)-Deoxyschizandrin (*cis*-5, 6, 7, 8-tetrahydro-1, 2, 3, 10, 11, 12-hexamethoxy-6, 7-dimethyldibenzo[*a,c*]cyclooctene) (**1**) is a constituent of the seed oil of *Schizandra chinensis* Bail (Magnoliaceae)<sup>1</sup> and is one among over 20 naturally occurring bis-benzocyclooctenes which are now classified as a subgroup of lignans. **1** along with other compounds isolated from *Schizandra sphenanthera* is useful for the treatment of virus-induced hepatitis<sup>2</sup>. Antihepatotoxic actions of deoxyschizandrin are also known<sup>3,4</sup>. The therapeutic activity of **1** has made it a synthetic target in recent times. Notable syntheses of this lignan include those of Kochetkov<sup>5</sup>, Ghera<sup>6</sup> and Stevenson<sup>7</sup>. 1,4-Bis(3, 4-dimethoxyphenyl)-2, 3-dimethylbutane (**2**), classified as a lignan, was recently isolated from the neutral fraction of the oil of *Myristica obo* fruits<sup>8</sup>. In this paper we report the syntheses of deoxyschizandrin (**1**) and the lignan (**2**).

It is known that (*E*)-2-*t*-butyl-3-phenyloxaziridine (**3**) reacts with Grignard reagents to afford the dimers in excellent yields<sup>9,10</sup>. The reaction occurs possibly through an electron transfer from the organometallic reagent to the oxaziridine followed by combination of free radical intermediates<sup>9</sup> (Eq. 1).



We envisioned that if we could synthesise the bromide (**10**), it can serve as a good intermediate to prepare **12**, which is the immediate precursor of **1** (Scheme 1).

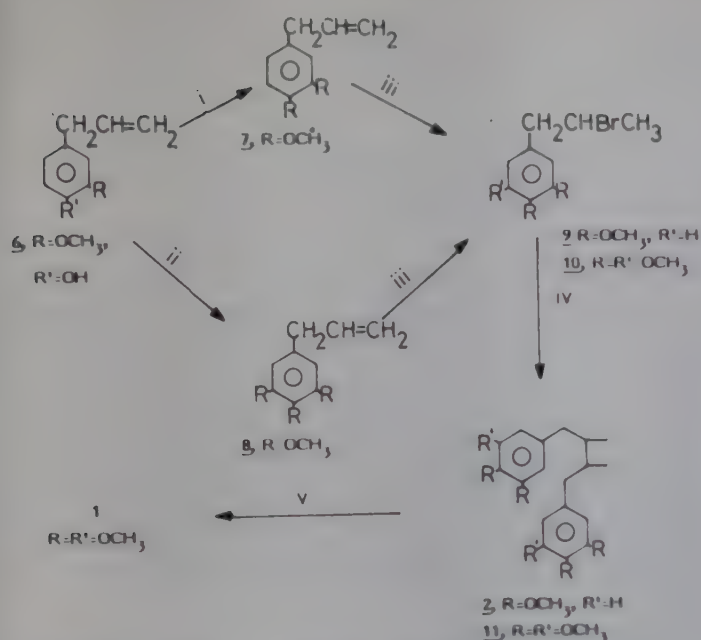
The nature of bromide (**10**) is secondary in contrast to the primary bromide utilised in the synthesis of brittonin A<sup>10</sup>. Hence 1-phenyl-2-bromopropane (**4**) which is devoid of three methoxyl groups in the aromatic nucleus was taken as a model compound and attempts were made to get the dimerised pro-



Scheme 2: Reagents and conditions: (i) ZnBr<sub>2</sub>/Al<sub>2</sub>O<sub>3</sub>, (ii) Mg/THF, 0°C, 3

duct, 1,4-diphenyl-2,3-dimethylbutane (**5**). **4** was prepared by the reaction of allyl bromide on benzene in the presence of zinc bromide and aluminium oxide. Grignard reagent of **4** in THF on reaction with **3** at 0°C afforded **5** in 84% yield (Scheme 2). With this as background 1-(3, 4, 5-trimethoxyphenyl)-2-bromopropane (**10**) was synthesised for the first time to be used in the synthesis of **1**.

The bromide (**10**) could be made easily by the hydrobromination of 1-allyl-3, 4, 5-trimethoxybenzene (**8**), which in turn was conveniently prepared starting from 4-allyl-2-methoxyphenol (**6**)<sup>11</sup>. (Both **8** and **6** are naturally occurring compounds known as elemicin and eugenol respectively). Addition of dry hydrogen bromide to a solution of **8** in glacial acetic acid at 0°C yielded **10** in 70% yield. Reaction of the Grignard reagent of **10** with **3** in THF at 0°C gave 1,4-bis(3, 4, 5-trimethoxyphenyl)-2,3-dimethylbutane (**11**) in 63% yield. Compound **11** on reaction with vanadium oxytrifluoride in methylene dichloride at -78° gave (±)-deoxyschizandrin (**1**) in 56% yield (Scheme 3).



Scheme 3: Reagents and conditions: (i) DMS/ $K_2CO_3$ , (ii) hexamine/ $AcOH$ ,  $H_2O_2$ , DMS, (iii)  $HBr/AcOH$ ,  $0^\circ C$ , (iv)  $Mg/THF$ ,  $0^\circ C$ , (v)  $VOF$ ,  $-78^\circ C$ .

The lignan (**2**) could be made similarly by the coupling of radicals generated from 1-(3,4-dimethoxyphenyl)-2-bromopropane (**9**). The bromide (**9**) was prepared by the addition of hydrogen bromide to 1-allyl-3,4-dimethoxybenzene (**7**) which was in turn prepared by methylating **6** using dimethyl sulphate. Addition of **3** to the Grignard reagent of **9** at  $0^\circ C$  resulted in **2**, as a colourless solid in 51% yield (Scheme 3).

### Experimental Procedure

Melting points are uncorrected. IR spectra were taken on a Perkin-Elmer model 298 spectrophotometer and PMR spectra on Varian EM 390 (90 MHz) and T-60 spectrometers with TMS as an internal standard. Column chromatography separation was carried out on BDH silica gel (60-120 mesh) with petroleum ether (60-80°)-benzene as solvent.

#### (E)-2-*t*-Butyl-3-phenyloxaziridine (**3**)

To a solution of benzylidene-*t*-butylimine (8.1 g, 0.05 mol) in  $CH_2Cl_2$  (25 ml) was added dropwise with stirring a solution of *m*-chloroperoxybenzoic acid (9.48 g, 0.055 mol) in  $CH_2Cl_2$  (50 ml) at  $0^\circ C$  during 4 hr. The reaction mixture was filtered and the filtrate washed with aq.  $Na_2SO_3$  and  $Na_2CO_3$  and dried ( $Na_2SO_4$ ). Solvent was removed and the residue distilled under reduced pressure to get **3**, yield 6.5 g (73%), b.p.  $107^\circ/1$  mm (lit.<sup>12</sup> b.p.  $61^\circ/0.03$  mm); PMR ( $CDCl_3$ ):  $\delta$  0.98 (s, 9H, *t*-butyl), 4.4 (s, 1H, PhCH), 7.18 (s, 5H,  $C_6H_5$ ).

#### Reaction between **3** and Grignard reagents:

##### General procedure

To a well stirred solution of Grignard reagent (1

mol) in dry THF, a solution of **3** (0.33 mol) in THF was added dropwise at  $0^\circ C$  under nitrogen atmosphere and stirred for 15 hr. The reaction mixture was hydrolysed with 5% HCl, extracted with ether, and the organic extract successively washed with water, saturated aq.  $NaHCO_3$ , water and dried ( $Na_2SO_4$ ). Solvent was removed under reduced pressure and product was separated through a column from petroleum ether-benzene.

#### 2-Bromo-1-phenylpropane (**4**)

Anhydrous zinc bromide (2 g) and aluminium oxide (1 g) were added to dry benzene (15 ml). To this was added allyl bromide (12.1 g) dropwise with constant stirring and the mixture was stirred at room temperature for 3 hr. Excess benzene was removed and the product distilled to give **4**, yield 15.5 g (77%); b.p.  $62^\circ/1$  mm, (lit.<sup>13</sup> b.p.  $112.5-14^\circ/20-21$  mm); IR: 3050, 2960, 2930, 1380,  $625\text{ cm}^{-1}$ ; PMR ( $CDCl_3$ ):  $\delta$  1.8 (*d*, 3H,  $CH_3$ ), 3.0-3.3 (*d*, 2H,  $CH_2$ ), 4.2-4.3 (*m*, 1H, CH), 7.3 (*s*, 5H,  $C_6H_5$ ).

#### 2,3-Dimethyl-1,4-diphenylbutane (**5**)

To the Grignard reagent made from magnesium turnings (0.48 g, 0.02 mol) and the bromide (**4**) (4 g, 0.02 mol) in dry THF was added **3** (1.18 g, 0.0066 mol) at  $0^\circ C$  and stirred for 15 hr. Work-up gave **5** as colourless liquid, yield 2.0 g (84%); b.p.  $96-97^\circ/0.1$  mm (lit.<sup>14</sup> b.p.  $118-22^\circ/0.5$  mm); IR: 3065, 2980, 1500,  $1460\text{ cm}^{-1}$ ; PMR ( $CDCl_3$ ):  $\delta$  0.90 (*d*, 6H,  $2 \times CH_3$ ), 1.45-1.85 (*m*, 2H,  $2 \times CH$ ), 2.10-2.70 (*m*, 4H,  $2 \times ArCH_2$ ), 6.70 (*s*, 10H,  $2 \times ArH$ ).

#### 1-Allyl-3,4,5-trimethoxybenzene (**8**)

This was made according to the procedure of Seshadri *et al*<sup>11</sup> from eugenol (**6**); b.p.  $106-7^\circ/1$  mm (lit.<sup>11</sup> b.p.  $148-49^\circ/10$  mm); PMR ( $CDCl_3$ ):  $\delta$  3.29 (*d*, 2H,  $ArCH_2$ ), 3.58 (*s*, 3H, 4- $OCH_3$ ), 3.65 (*s*, 6H, 3,5- $OCH_3$ ), 4.8-5.1 (*m*, 2H,  $CH=CH_2$ ), 5.45-6.0 (*m*, 1H,  $CH=CH_2$ ), 6.4 (*s*, 2H,  $ArH$ ).

#### 1-(3,4,5-Trimethoxyphenyl)-2-bromopropane (**10**)

Dry HBr, generated by adding bromine to dry tetralin, was passed through two columns containing tetralin and conc.  $H_2SO_4$  and led into a solution of **8** (6.24 g, 0.03 mol) in glacial acetic acid (20 ml) at  $0^\circ C$ . After saturating the reaction mixture (30 min) with HBr, the reaction mixture was kept at  $0^\circ C$  for another 3 hr with stirring. It was then poured into ice and water, extracted with benzene, the organic extract washed successively with water, saturated aq.  $NaHCO_3$  and dried ( $K_2CO_3$ ). Benzene was removed and the bromide (**10**) was distilled under reduced pressure, yield 6.1 g (70%); b.p.  $155^\circ/2$  mm (Found: C, 49.7; H, 5.8,  $C_{12}H_{17}O_3Br$  requires C,

49.8; H, 5.9%); IR 2930, 2850, 1595, 1460, 1420, 1380, 1250, 1150, 1040, 950, 920, 850, 580  $\text{cm}^{-1}$ ; PMR ( $\text{CDCl}_3$ ):  $\delta$  1.7 (*d*, 3H,  $\text{CH}_3$ ), 3.0-3.3 (*d*, 2H,  $\text{CH}_2$ ), 3.7 (*s*, 6H,  $2 \times \text{OCH}_3$ ), 3.75 (*s*, 3H,  $\text{OCH}_3$ ), 3.9-4.2 (*m*, 1H, CH), 6.7 (*s*, 2H,  $\text{C}_6\text{H}_2$ ).

1,4-Bis-(3,4,5-trimethoxyphenyl)-  
2,3-dimethylbutane (**11**)

To the Grignard reagent made from magnesium turnings (0.24 g, 0.01 mol) and **10** (2.89 g, 0.01 mol) in dry THF and cooled to  $0^\circ\text{C}$ , was added **3** (0.59 g, 0.0033 mol) in dry THF and stirred for 15 hr. Work-up gave the diaryl butane (**11**) as a colourless solid, yield 63%, m.p.  $86-87^\circ$  (lit.<sup>7</sup> m.p.  $87-89^\circ$ ); PMR ( $\text{CDCl}_3$ ):  $\delta$  0.86 (*d*, 6H,  $2 \times \text{CH}_3$ ), 1.40-1.90 (*m*, 2H,  $2 \times \text{CH}$ ), 2.20-2.80 (*m*, 4H,  $2 \times \text{ArCH}_2$ ), 3.81 (*s*, 18H,  $6 \times \text{ArOCH}_3$ ), 6.40 (*s*, 4H,  $2 \times \text{C}_6\text{H}_2$ ).

( $\pm$ )-Deoxyschizandrin (**1**)<sup>7</sup>

Trifluoroacetic acid (2 ml) and  $\text{CH}_2\text{Cl}_2$  (8 ml) were added to a solution of **11** (80 mg, 0.00019 mol) in  $\text{CH}_2\text{Cl}_2$  at  $-78^\circ\text{C}$  and stirred for 10 min. Vanadium oxytrifluoride (150 mg) was then added and stirred at the same temperature for 30 min and at room temperature for another 30 min. Solvent was removed and conc.  $\text{NH}_4\text{OH}$  solution (5 ml) was added and the mixture was extracted with ether. Evaporation of the washed and dried organic extract gave a solid, which was crystallised from methanol to get **1**, yield 45 mg (56%), m.p.  $113-14^\circ$  (lit.<sup>6</sup>  $112-13^\circ$ ); PMR ( $\text{CDCl}_3$ ):  $\delta$  0.8 (*d*, 3H,  $s\text{-CH}_3$ ), 1.0 (*d*, 3H,  $s\text{-CH}_3$ ), 1.8-2.05 (*m*, 2H,  $\text{H}_6$  &  $\text{H}_7$ ), 2.10-2.60 (*m*, 4H,  $2 \times \text{ArCH}_2$ ), 3.55 (*s*, 6H,  $2 \times \text{ArOCH}_3$ ), 3.85 (*s*, 12H,  $4 \times \text{ArOCH}_3$ ), 6.45 (*s*, 2H,  $2 \times \text{ArH}$ ).

1-Allyl-3,4-dimethoxybenzene (**7**)

To eugenol (**6**) (16.42 g, 0.1 mol) and anhydrous  $\text{K}_2\text{CO}_3$  (30 g) in dry acetone was added freshly distilled dimethyl sulphate (30 g) and refluxed for 6 hr. Usual work-up and distillation under reduced pressure gave **7**, yield 13.6 g (76%), b.p.  $75^\circ/1 \text{ mm}$  (lit.<sup>15</sup>  $128-29^\circ/11 \text{ mm}$ ).

1-(3,4-Dimethoxyphenyl)-2-bromopropane (**9**)

Dry hydrogen bromide was generated and led into a solution of **7** (5.34 g, 0.03 mol) in glacial acetic acid (5 ml) at  $0^\circ\text{C}$  and worked-up as mentioned in the preparation of **10** to get **9**, yield 5.1 g (65%), b.p.  $113-15^\circ/0.5 \text{ mm}$  (lit.<sup>16</sup>  $171-72^\circ/10 \text{ mm}$ ); PMR

( $\text{CDCl}_3$ ):  $\delta$  1.7-1.8 (*d*, 3H,  $\text{CH}_3$ ), 2.8-3.1 (*t*, 2H,  $\text{CH}_2$ ), 3.8 (*s*, 6H,  $2 \times \text{OCH}_3$ ), 4.0-4.3 (*m*, 1H, CH), 6.7 (*s*, 3H,  $3 \times \text{ArH}$ ).

1,4-Bis-(3,4-dimethoxyphenyl)-  
2,3-dimethylbutane (**2**)

Grignard reagent was made from magnesium turnings (0.24 g, 0.01 mol) and **9** (2.59 g, 0.01 mol) in dry THF under dry nitrogen atmosphere and cooled to  $0^\circ\text{C}$ . To this was added with stirring a solution of **3** (0.59 g, 0.0033 mol) in dry THF (2 ml) and stirred for 15 hr. Work-up gave **2** as colourless solid, yield 0.93 g (51%), m.p.  $98-99^\circ$  (lit.<sup>17</sup> m.p.  $100-101^\circ$ ); PMR ( $\text{CDCl}_3$ ):  $\delta$  0.85 (*d*, 6H,  $2 \times \text{CH}_3$ ), 1.5-1.8 (*m*, 2H,  $2 \times \text{CH}$ ), 2.2-2.7 (*m*, 4H,  $2 \times \text{ArCH}_2$ ), 3.8 (*s*, 12H,  $4 \times \text{OCH}_3$ ), 6.6-6.8 (*m*, 6H,  $2 \times \text{ArH}$ ).

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# Confirmation of Structure of Isosolacapsine: Stereochemistry at Ring Junctionure of Indolizidine Moiety of 22 $\beta$ H Solanidanes by $^{13}\text{C}$ & $^1\text{H}$ NMR Spectroscopy†

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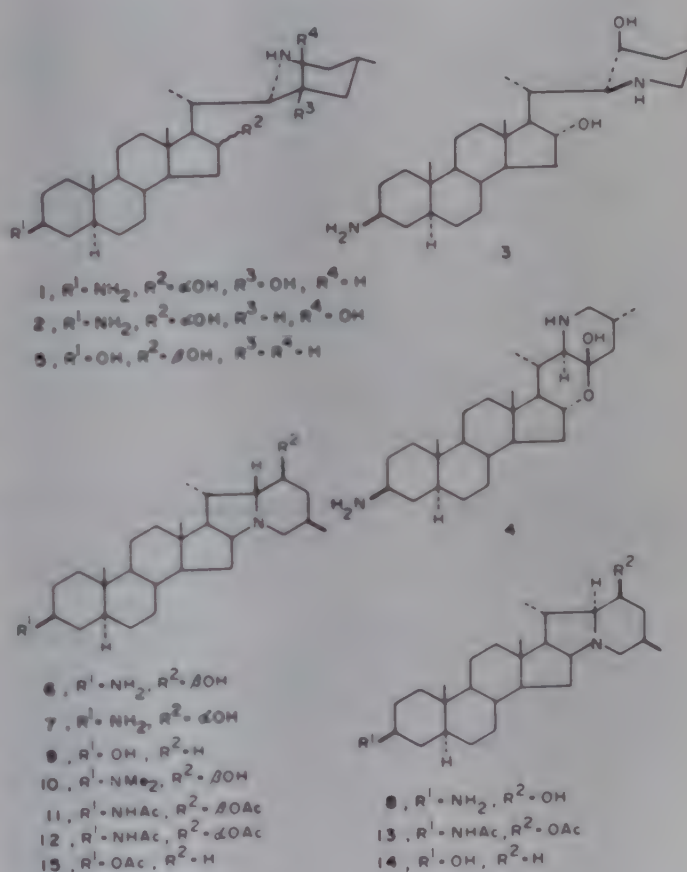
Isosolacapsine, a minor steroidal alkaloid of *Solanum pseudocapsicum*, earlier assigned structure **3**, possesses a novel 22  $\beta$  N stereochemistry in a 22,26-epimincholestane skeleton. This alkaloid has now been isolated from *Solanum capsicastrum* and its structure confirmed by its conversion to solanogantamine (**8**), a 22  $\alpha$ H solanidane derivative ex *Solanum giganteum*. The ring-juncture stereochemistry of the indolizidine moiety of 22  $\beta$  H solanidanes, in general, has been elucidated on  $^{13}\text{C}$  and  $^1\text{H}$  NMR spectral evidences.

We earlier reported<sup>1</sup> the isolation of three stereoisomeric 3-amino-22, 26-epimincholestanes, viz. solacapsine (**1**), episolacapsine (**2**) and isosolacapsine (**3**) from *Solanum pseudocapsicum* Linn. While **1** and **2** were characterised by chemical correlation with solanocapsine (**4**), isosolacapsine was assigned structure **3** with a novel 22  $\beta$ -N stereochemistry with axially oriented 23-OH and 25-Me groups mainly on the basis of  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectral analyses.

In course of our recent investigations<sup>2,3</sup> on *S. capsicastrum* Linn, we encountered isosolacapsine (**3**) also as a minor constituent which enabled us to confirm its tentative structure. Furthermore, the stereoisomeric alkaloids (**1-3**) as well as tetrahydrosolasodine-A (**5**)<sup>4</sup> were converted into the corresponding solanidanes (**6-9**) and the  $^{13}\text{C}$  and  $^1\text{H}$  NMR spectra of these compounds and some of their derivatives were studied with a view to establishing their stereochemistry at the E/F ring junctions.

We have already shown<sup>5</sup> that solacapsine (**1**), a 22  $\alpha$ N-22,26-epimincholestane, on  $\text{CrO}_3$  oxidation followed by  $\text{NaBH}_4$  reduction leads to solanogantamine (**6**), the only naturally occurring 22  $\beta$ H solanidane derivative isolated<sup>5</sup> in this laboratory from *S. giganteum* Jacq. Under the same conditions, **2**, **3** and **5** gave the respective solanidane derivatives **7**, **8** and **9** in 30-50% yields.

Compound **8** was found to be identical ( $^{13}\text{C}$  and  $^1\text{H}$  NMR) with solanogantamine<sup>1,6</sup>, a 22  $\alpha$  H solanidane derivative ex *S. giganteum* thereby confirming the structure and stereochemistry of isosolacapsine (**3**) proposed by us<sup>1</sup>.



In order to have an insight into the stereochemistry of the indolizidine ring system of 22  $\beta$  H solanidanes,  $^{13}\text{C}$  NMR spectra of some 22  $\alpha$ H and 22  $\beta$  H compounds and some of their derivatives, viz. 3-N,N-dimethylsolanogantamine (**10**), N,O-diacetylsolanogantamine (**11**), **7** and its N,O-diacetate (**12**), **8** and its N,O-diacetate (**13**), **9** and demissidine (**14**) were analysed. The  $^{13}\text{C}$  chemical shifts of these compounds are compiled in Table 1.

It can be seen from the data in Table 1 that, in general, most of the carbon signals of D, E and F

†Part 88 in the series. For Part 87, see Mukhopadhyay R, Ghosh Dastidar PP, Ali E & Pakrashi S C, *J natural Prod.* (In press).

Table 1—Carbon-13 Chemical Shifts<sup>a</sup> of Some Solanidane Derivatives

Carbon No.	7	8 <sup>b</sup>	9	10	11	12	13	14
1	37.6	36.9	36.9	37.5	37.2	37.4	37.4	37.1
2	30.4	31.3	31.3	24.3	28.4	28.5	28.5	31.6
3	51.0	50.9	70.7	63.8	48.8	48.9	48.9	71.3
4	39.2	39.	38.0	30.8	35.2	35.5	35.4	38.3
5	45.6	45.6	44.7	45.5	45.3	45.4	45.3	45.0
6	28.7	28.6	28.6	28.8	28.2	28.8	28.8	28.8
7	32.4	32.1	32.3	32.4	32.1	32.3	32.0	32.3
8	34.7	35.2	34.5	34.1	34.4	35.0	35.4	35.4
9	54.5	54.5	54.3	54.3	54.1	54.3	54.3	54.6
10	35.6	35.5	35.4	35.7	35.4	35.5	35.4	35.6
11	21.1	20.8	21.1	20.9	21.0	21.1	20.8	21.1
12	40.5	39.5	40.6	40.5	40.3	40.6	39.7	40.2
13	41.1	41.3	40.9	41.5	41.3	40.9	41.2	40.6
14	56.4	57.3	56.1	54.2	55.0	56.9	57.2	57.4
15	29.6	32.4	29.8	26.7	28.4	29.6	31.4	33.5
16	66.5	69.3	66.1	66.4	65.3	65.6	68.5	69.0
17	62.7	62.1	61.2	60.9	61.3	63.3	62.0	63.3
18	16.0	16.6	15.1	14.8	15.1	15.1	16.3	17.1
19	12.3	12.2	12.2	12.2	12.1	12.2	12.1	12.4
20	34.4	30.4	34.5	33.2	33.6	33.6	30.8	36.7
21	16.3	18.6	16.0	17.4	16.8	16.6	18.9	18.3
22	69.2	78.8	64.0	70.4	67.5	67.8	76.5	74.7
23	66.7	66.6	23.5	67.7	70.0	70.5	68.5	29.3
24	41.1	37.1	33.3	43.2	39.1	37.4	34.0	31.3
25	19.4	26.8	25.3	29.3	27.3	18.2	27.2	31.3
26	54.3	58.5	54.8	54.7	54.2	53.8	57.2	60.2
27	19.0	22.0	19.0	18.9	18.5	18.9	20.4	19.5
NMe <sub>2</sub>	—	—	—	41.5	—	—	—	—
NCOCH <sub>3</sub>	—	—	—	—	23.1	23.4	23.4	—
NCOCH <sub>3</sub>	—	—	—	—	169.7	170.1	170.9	—
OCOCH <sub>3</sub>	—	—	—	—	21.0	21.9	21.2	—
OCOCH <sub>3</sub>	—	—	—	—	168.8	169.1	169.2	—

<sup>a</sup>Spectra were recorded in CDCl<sub>3</sub> and the chemical shifts are expressed in  $\delta$ -scale from TMS.<sup>b</sup>Data incorporated from ref. 1.

rings of 22 $\beta$  H solanidanes (**7**, **9**, **10-12**) invariably suffered upfield shift as against those of 22 $\alpha$  H compounds (**8**, **13**, **14**) presumably due to the ring strain. The diagnostic ones were, however, found to be those for C-15 (2-4 ppm), C-16 (2-3 ppm), C-22 (9-11 ppm) and C-26 (4-5 ppm). The more or less consistent up-field shift of the signals for those carbons in the vicinity of the indolizidine nitrogen clearly demonstrated that the E/F ring fusion is the same in all the 22 $\beta$  H solanidanes studied irrespective of the presence of substituent at C-23.

We earlier demonstrated<sup>5</sup> by spin-decoupling experiment that the 16 $\alpha$ -H of solanogantine (**6**) resonated downfield ( $\delta$  3.69 in **10** and 3.64 in **11**) compared to 22 $\beta$ -H ( $\delta$  2.25 in **10** and 2.61 in **11**) because of its *cis* relationship with the nitrogen lone pair. Accordingly, the indolizidine ring system of **6** was proposed to have *trans* ring fusion which was also supported by mercuric acetate oxidation. Since

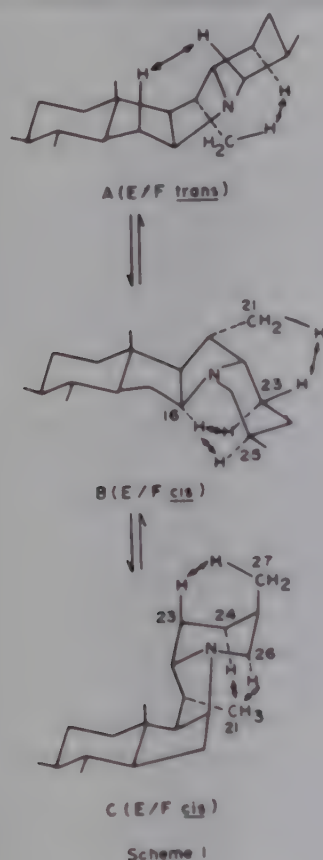
the <sup>1</sup>H NMR spectra of **9**, **12** and **15** exhibited similar lowfield signals for their 16 $\alpha$ -H at  $\delta$  3.65 (Table 2), it could be inferred that all the 22 $\beta$  H solanidanes studied possess *trans* indolizidine ring system (conformation A in Scheme 1). Compound **9**, however, has earlier been reported<sup>7,8</sup> to possess a *cis*-fused indolizidine ring system on the basis of IR spectra<sup>7</sup> and reaction with mercuric acetate<sup>8</sup>. In such a case, C-16 should have experienced two  $\gamma_g$  interactions with C-23 and C-25 in its sterically more stable conformer B (Scheme 1) which was, in fact, not reflected in its <sup>13</sup>C chemical shifts (Table 1). We could, however, confirm the reported<sup>8</sup> sluggish oxidation of **9** with mercuric acetate contrary to the fast reaction in case of solanogantine (**6**) and its derivative (**11**). The reason for this anomaly is not readily understood.

On the basis of the above observations, it can be reasonably concluded that E/F ring system of 22 $\beta$  H solanidanes is *trans*-fused.

Table 2— $^1\text{H}$  Chemical Shifts\* of Some  $22\beta$  H Solanidanones

Compd	10-Me & 13-Me	20-Me	25-Me	3-H	16-H	22-H	23-H	26-Heq	Others
9	0.80	0.85d (7)	0.78d (7)	3.40 -3.75m	3.40 -3.75m	—	—	2.78m	—
10 <sup>s</sup>	0.78	1.01d (7)	0.88d (7)	—	3.69m	2.25m	3.5m $w\ddagger = 23$ Hz	2.78d (10)	2.30 (NMe <sub>2</sub> )
11 <sup>s</sup>	0.80	0.86d (7)	0.83d (7)	3.64m	3.64m	2.61dd (10,6)	4.64ddd (10,9,4)	2.78d (10)	1.93 (NAc), 2.01 (OAc)
12	0.78, 0.83	0.86d (7)	0.83d (7)	3.40 -4.00m	3.40 -4.00m	3.16dd (7,3)	4.90m ( $w\ddagger = 7$ Hz)	—	1.92 (NAc), 2.05 (OAc), 5.44 (CONH)
15	0.81	0.86d (7)	0.78d (7)	4.68m	3.63m	—	—	2.83d (10)	2.00 (OAc)

\*Spectra were recorded in  $\text{CDCl}_3$  and the chemical shifts are expressed in  $\delta$ -scale with TMS as an internal standard. Figures in parentheses are the coupling constants in Hz.



dividual signals to specific carbons were done on the basis of selective proton decoupling experiments (where applicable) and by comparison with the reported data<sup>1</sup> in similar systems.

#### General procedure for conversion of 16-hydroxy-22,26-epiminocholestanes to solanidanones

In a typical experiment, to a solution of **1** (0.001 mol) in freshly distilled glacial AcOH (15 ml), a solution of  $\text{CrO}_3$  (0.001 mol) in the same solvent (15 ml) was added dropwise with constant stirring at room temperature. After completion of addition, the reaction mixture was stirred for 2 hr more and kept at room temperature for 16 hr. It was diluted with water (100 ml), basified with  $\text{NH}_3$  solution and extracted with  $\text{CHCl}_3$  to get the crude carbinolamine. It was dissolved in ethanol (20 ml) and reduced with excess  $\text{NaBH}_4$  at room temperature for 12 hr. Usual work-up gave **6** as amorphous material which was purified through the preparation of acetate at room temperature followed by chromatography over neutral alumina to get N,O-diacetylsolanogantane (**11**)<sup>5</sup> in 50% yield.

Incidentally, though the  $^{13}\text{C}$  and  $^1\text{H}$  NMR spectral data of some  $22\alpha$  H solanidanones are available in the literature<sup>1,9</sup>, to the best of our knowledge, none except  $^1\text{H}$  NMR data<sup>6</sup> of **6** is reported so far for  $22\beta$  H isomers.

#### Experimental Procedure

$^1\text{H}$  and  $^{13}\text{C}$  NMR spectra were recorded in  $\text{CDCl}_3$  on a JEOL FX-100 FT NMR spectrometer at 100 MHz and 25 MHz respectively and the chemical shifts are expressed in  $\delta$ -scale from TMS as an internal standard. The multiplicities of the individual signals in  $^{13}\text{C}$  NMR spectra were ascertained on the basis of INEPT experiments. The assignments of in-

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# Conformational Analysis of 1,1,2-Trisubstituted Ethanes by PMR: Part II—3-Aryl-2-methyl-1-propyl Halides

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Precise conformational analysis about the  $C_1-C_2$  bond has been made in ten compounds of the general structure  $R-CH_2-CHMe-CH_2-X$ , where  $R$  = phenyl (5),  $p$ -nitrophenyl (3),  $p$ -methoxyphenyl (1) or  $t$ -butyl (1), and  $X$  = chloro (4), bromo (2), iodo (1), methoxy (2) or amino (1). Weak intramolecular interactions between the  $CH_2-X$  dipole and the aromatic  $\pi$  electrons are proposed in order to explain the calculated relative enthalpies and entropies of the two major conformers, in the halo compounds. The nonaromatic compound ( $R = t$ -butyl,  $X =$  chloro) shows abnormally low vicinal coupling constants, and both vicinal coupling constants increase with temperature; large deviations from staggeredness account for the magnitudes of the coupling constants, and increased amplitudes of torsional vibrations causing new ensembled averages of  $\cos^2 \phi$  results in enhanced coupling.

A self-consistent model for the conformational analysis of 1,1,2-trisubstituted ethanes, based on the Karplus relation for vicinal coupling constant as a function of the dihedral angle, has been reported<sup>1</sup>. The model has been used to evaluate the effects of solvents and concentration on conformational free energies<sup>1</sup>.

Detailed variable-temperature studies on a series of model compounds are reported here, to establish the effect of weak intramolecular interactions on conformational enthalpies and entropies. Large deviations from staggeredness and their repercussions on the observed spectral parameters are also dealt with here.

## Materials and Methods

The NMR techniques employed and the model (including the algorithm) developed for conformational analysis are already reported<sup>1</sup>.

The following compounds were prepared employing literature methods: (i) 1-chloro-2-methyl-3-phenylpropane, (ii) 1-chloro-3-(4-methoxyphenyl)-2-methylpropane, (iii) 1-chloro-2-methyl-3-(4-nitrophenyl)propane, (iv) 1-bromo-2-methyl-3-phenylpropane, (v) 1-bromo-2-methyl-3-(4-nitrophenyl)propane, (vi) 1-iodo-2-methyl-3-phenylpropane, (vii) 1-methoxy-2-methyl-3-phenylpropane, (viii) 1-methoxy-2-methyl-3-(4-nitrophenyl)propane, (ix) 2-methyl-3-phenyl-1-propylamine and (x) 1-chloro-2, 4, 4-trimethylpentane. The purity of all these compounds was checked by GLC and PMR.

## Results and Discussion

### 3-Aryl-2-methyl-1-propyl halides

Results of the variable-temperature studies for 1-chloro-2-methyl-3-(4-nitrophenyl)propane are given in Tables 1 and 2, other compounds give similar results. These are summarized in Table 3:

#### (i) Intramolecular interaction

It is shown (*vide infra*) that the *trans* form is the most stable conformer in  $Me_3C-CH_2-CHMe-CH_2Cl$ , in spite of electrostatic attraction possible in the *gauche* rotamer. This indicates that, sterically, chloromethyl is larger than methyl. This conclusion is independent of the specific compound. Thus, if *t*-butyl is replaced by a smaller group, the energy difference between the *trans* and *gauche* forms is likely to decrease, but the *gauche* can never be of lower energy than *trans*, unless there is intramolecular interaction stabilizing it (Fig. 1).

The fact that the enthalpies of the *gauche* forms are lower than those of the *trans* in all six halides

Table 1—Temperature-dependence of Spectral Parameters for  $p\text{-NO}_2-C_6H_4-CH_2-CHMe-CH_2Cl$  in Chloroform Solution (0.33 M)

Temp (°C)	$\Delta\nu$ (ppm)	$J_a$ (Hz)	$J_b$ (Hz)	$J_s$ (Hz)	$J_{gem}$ (Hz)
105.8	0.3069	7.777	6.565	14.342	-14.008
87.2	0.3086	7.758	6.575	14.333	-13.868
66.4	0.3100	7.756	6.622	14.378	-13.875
45.6	0.3104	7.679	6.703	14.382	-13.847
12.3	0.3117	7.785	6.773	14.558	-13.695
-11.8	0.3112	7.717	6.929	14.646	-13.714
-30.1	0.3108	7.704	6.962	14.666	-13.588
-45.3	0.3095	7.669	7.101	14.770	-13.575

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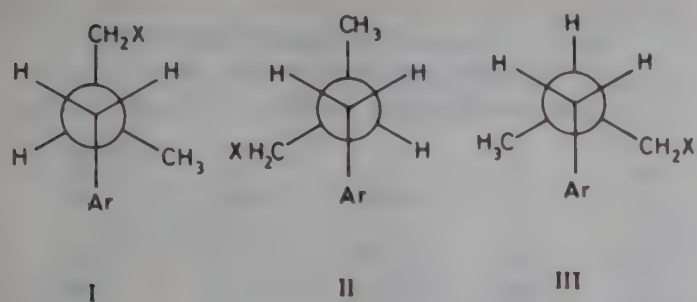


Fig. 1—Three Conformers of  $\text{Ar}-\text{CH}_2-\text{CHMe}-\text{CH}_2\text{X}$ , *trans* (I), *gauche* (II) and *gauche-gauche* (III)

Table 2—Conformational Analysis about  $\text{C}_2-\text{C}_3$  Bond of  $p\text{-NO}_2-\text{C}_6\text{H}_4-\text{CH}_2-\text{CHMe}-\text{CH}_2\text{Cl}$

Temp. (K)	$n_1$	$n_2$	$n_3$	$\Delta G$ (cal/mol)	$\Delta H$ (cal/mol)
378.8	0.534	0.422	0.044	177	-144
360.2	0.532	0.423	0.045	165	-141
339.4	0.532	0.427	0.041	148	-140
318.6	0.525	0.435	0.041	119	-150
285.3	0.535	0.441	0.024	109	-133
261.1	0.528	0.455	0.016	77	-144
242.9	0.527	0.458	0.014	67	-139
227.7	0.524	0.471	0.005	47	-145

$$\Delta H^\circ = -142 \pm 12 \text{ cal/mol};$$

$$\Delta S^\circ = -0.849 \pm 0.040 \text{ cal/deg/mol.}$$

Table 3—Energy Differences between Conformers I and II in  $p\text{-R}-\text{C}_6\text{H}_4-\text{CH}_2-\text{CHMe}-\text{CH}_2-\text{R}'$

R	R'	$\Delta H$ (cal/mol)	$\Delta S$ (cal/deg/mol)	$\Delta G_{25}$ (cal/mol)
$\text{NO}_2$	OH	393	0.234	323
H	OH	305	0.198	246
MeO	OH	301	0.256	225
$\text{NO}_2$	Cl	-142	-0.849	111
H	Cl	-211	-0.852	43
MeO	Cl	-178	-0.653	17
$\text{NO}_2$	Br	-209	-0.971	80
H	Br	-205	-0.735	14
H	I	-178	-0.706	32
$\text{NO}_2$	OMe	248	-0.202	308
H	OMe	172	-0.402	292
H	$\text{NH}_2$	173	-0.212	237
( <i>t</i> -Bu)	Cl	185	-0.539	346)*

\*Compound is  $\text{Me}_3\text{C}-\text{CH}_2-\text{CHMe}-\text{CH}_2\text{Cl}$

shows that the electrostatic attraction between halogens and aryl groups more than offsets the steric repulsions.

The extent of interactions may be estimated, based on the following approximations. The difference between methyl and chloromethyl must be similar to the difference between methyl and other  $-\text{CH}_2\text{R}'$  groups listed in Table 3. The mean  $\Delta H$  in these compounds is  $+265 \pm 99$  cal/mol. Since the

corresponding value in the six halides is  $-187 \pm 39$  cal/mol, the intramolecular interaction must be of the order of  $452 \pm 138$  cal/mol.

The entropy for the equilibrium between conformers I and II is  $-0.8 \pm 0.1$  in the halides. This negative value is another piece of evidence for the presence of intramolecular interaction (*vide infra*).

#### (ii) Significance of the entropy difference

Mizushima *et al.*<sup>2</sup> have suggested that the entropy difference between rotational isomers arises mainly from the difference in the internal rotation about the single bonds. Mizushima *et al.*<sup>3</sup> have also observed that the frequencies of the torsional oscillations are likely to become higher, due to internal H-bonding. This will make the entropy of the bonded rotamer considerably lower than the non-bonded one.

In all six halides under study, the *gauche* forms are lower in entropy by 0.8 cal/deg/mol. This must be arising from the partial loss of freedom to rotation about  $\text{C}_1-\text{C}_2$  and  $\text{C}_2-\text{C}_3$  bonds, caused by intramolecular interaction. The second factor, namely the higher frequency of torsional oscillation caused by internal attraction, might be a minor contributor<sup>4</sup>.

The slightly negative values for the amine and the two ethers (Table 3) can be attributed to very weak intramolecular interaction. The enthalpy values lend support to this inference.

#### (iii) Nature of aryl-halogen interactions

As can be seen from Table 3, the conformational stability of the halides exhibits no great change or regular trend when going from chloride to iodide, or when going from *p*-methoxy to *p*-nitro. Similarly, the entropy differences for the six halides are very much alike.

It may be recalled that the dipole moments of methyl chloride, bromide and iodide are 1.87D, 1.81D and 1.62D, respectively<sup>5</sup>. It is thus reasonable to visualize an electrostatic attractive force between the polar C-X group and the polarizable  $\pi$ -cloud of the aryl system. The attraction could also be of the nature of London dispersion forces, between the aromatic ring and the halogen.

#### (iv) Consistency of Karplus constants

The Karplus constants employed in the conformational analysis, computed as depicted earlier<sup>1</sup> are listed in Table 4. A change from  $\text{MeO}-\text{C}_6\text{H}_4-$  to  $\text{C}_6\text{H}_5-$  to  $\text{NO}_2\text{C}_6\text{H}_4-$  in the substrate hardly causes a variation in the magnitude of these parameters; nor does an alteration from  $-\text{OH}$  to  $-\text{OMe}$  to  $-\text{NH}_2$  to  $-\text{Cl}$  to  $-\text{Br}$  to  $-\text{I}$  have any profound influence on them.

This internal consistency, we feel, may advantageously be used to diagnose departures from staggeredness. Thus, deviations, caused by repulsive or attractive interactions, will be reflected in the magnitude of these parameters.

Such a situation is exemplified by the low values of  $J_+$  and Karplus constants for  $\text{Me}_3\text{C}-\text{CH}_2-\text{CHMe}-\text{CH}_2\text{Cl}$  (Table 4). In all probability, the equilibrium dihedral angles are distorted from the normal values in this case.

*Me<sub>3</sub>C-CH<sub>2</sub>-CHMe-CH<sub>2</sub>Cl, a model compound*

The results of variable-temperature studies (Table 5) are of particular interest in this case. Both  $J_a$  and  $J_b$  increase noticeably with temperature. These observations are, by no means, novel; and such results have led to unwanted conclusions in the past<sup>6,7</sup>.

Depletion of population in conformation III, along with augmentation in I and II, is the easiest explanation for the observed trend. In addition, if it is assumed that there is no sizable entropy term, the variations in populations will have to be attributed to new Boltzmann distributions. This will lead to the conclusion that conformer III is more stable than the other two.

In cases like this, 'direct search' computations<sup>8</sup> have been employed, in which the Karplus constants and conformational energies are independently varied to obtain the best match between the observed and calculated values of coupling constants<sup>6,7</sup>. In order to emulate this technique, and to take into account the magnitude as well as the rate of change of the vicinal coupling constants, we started changing the magnitude of the Karplus constants systematically, keeping their ratio constants. The convergence test was the sum of the absolute magnitude of the entropy terms for the three equilibria, the least value of this being the best match. The convergence here is with the *gauche-gauche* as the most stable conformer, with the *trans* and *gauche* above this by 233 cal/mol and 480 cal/mol, respectively.

Conformational analysis based on this are given in Table 6. These values are in excellent agreement with the results of Cavanaugh<sup>6,7</sup> and Pachler<sup>9</sup> for the conformational analysis of phenylalanine. However, it is essential to envision an attractive interaction of 2.0-2.5 kcal/mol between the methyl and *t*-butyl groups to make conformer III more stable than II. Such an interaction is never experimentally detected before, nor is its possibility ever deemed plausible. Hence these results are dismissed as being spurious, and alternate explanations sought.

(i) *Deviations from staggeredness*

This is an attractive alternative, considering the bulkiness of the *t*-butyl group. The comparative yel-

Table 4—Karplus Constants Employed in Conformational Analysis of  $p\text{-R}-\text{C}_6\text{H}_4-\text{CH}_2-\text{CHMe}-\text{CH}_2-\text{R}'$

R	R'	$J_+$ (Hz)	$J_0$ (Hz)	$J'_0$ (Hz)
NO <sub>2</sub>	OH	14.355	12.674	7.921
H	OH	14.354	12.696	7.935
MeO	OH	14.395	12.738	7.961
NO <sub>2</sub>	Cl	14.558	12.883	8.052
H	Cl	14.408	12.771	7.982
MeO	Cl	14.331	12.743	7.964
NO <sub>2</sub>	Br	14.674	13.025	8.140
H	Br	14.017	12.462	7.789
H	I	14.456	12.916	8.073
NO <sub>2</sub>	OMe	14.252	12.678	7.924
H	OMe	14.298	12.771	7.982
H	NH <sub>2</sub>	14.310	12.852	8.033
<i>t</i> -Bu	Cl	10.180	9.111	5.694*
Mean $\pm$ SE†		14.367 $\pm 0.155$	12.767 $\pm 0.137$	7.980 $\pm 0.086$

\*Compound is  $\text{Me}_3\text{C}-\text{CH}_2-\text{CHMe}-\text{CH}_2\text{Cl}$

Table 5—Temperature-dependence of Spectral Parameters for  $\text{Me}_3\text{C}-\text{CH}_2-\text{CHMe}-\text{CH}_2\text{Cl}$  in Chloroform Solution (0.33 M)

Temp. °C	$\Delta \nu$ (ppm)	$J_a$ (Hz)	$J_b$ (Hz)	$J_c$ (Hz)	$J_{\text{gem}}$ (Hz)
107.9	0.2916	6.216	4.284	10.500	-14.339
87.8	0.2872	6.170	4.218	10.388	-14.328
66.9	0.2816	6.172	4.236	10.408	-14.287
46.2	0.2767	6.185	4.086	10.271	-14.301
28.9	0.2719	6.149	4.031	10.180	-14.250
9.3	0.2660	6.084	3.981	10.065	-14.274
-11.5	0.2576	6.042	3.917	9.959	-14.288
-31.0	0.2489	6.055	3.822	9.877	-14.238

$\Delta H^\circ = 185 \pm 20$  cal/mol;

$\Delta S^\circ = -0.539 \pm 0.066$  cal/deg/mol.

Table 6—Conformational Analysis\* about C<sub>2</sub>-C<sub>3</sub> Bond of  $\text{Me}_3\text{C}-\text{CH}_2-\text{CHMe}-\text{CH}_2\text{Cl}$

Temp. (K)	$n_1$	$n_2$	$n_3$	$\Delta G(2)$ (cal/mol)†
380.9	0.383	0.207	0.410	-519
360.8	0.379	0.201	0.420	-531
339.9	0.379	0.202	0.419	-491
319.2	0.380	0.188	0.431	-525
301.9	0.377	0.183	0.439	-524
282.3	0.371	0.179	0.450	-517
261.5	0.367	0.173	0.460	-508
242.0	0.369	0.164	0.467	-502

\*This is based on the assumption that entropy difference between the conformers is not significant.

†For the equilibrium between conformers II and III.

low values of  $J_+$  (Tables 4 and 5) add credence to this surmise (*vide supra*).

Accordingly, we investigated possible variations in the 'apparent equilibrium dihedral angles' by solving Eqs. (1) and (2):

$$J_a = J_0 n_1 \cos^2(180 - x) + J'_0 n_2 \cos^2(60 + y) + J'_0 n_3 \cos^2(60 - x + y) \quad \dots (1)$$

$$J_b = J_0 n_1 \cos^2(60 + x) + J_0 n_2 \cos^2(180 - y) + J'_0 n_3 \cos^2(60 + x - y) \quad \dots (2)$$

Here,  $J_0$  and  $J'_0$  are the mean of the Karplus constants employed in the previous instances (Table 4);  $n_1$ ,  $n_2$  and  $n_3$  at each temperature are derived from the calculated  $\Delta G$  at ambient temperature, neglecting possible entropy contributions; and  $x$  and  $y$  are the deflections from normalcy in the *trans* and *gauche* forms respectively. The results are compiled in Table 7.

#### (ii) Form of the potential function<sup>10-12</sup>

In a symmetrical coaxial top like 1,1,1-trichloroethane the potential energy should vary as a function of the angle between the HCC and the CCl planes. If  $\phi$  represents the angle of rotation, the potential  $U(\phi)$  is expressed by Eq. (3):

$$U(\phi) = 1/2 U_0 (1 - \cos n\phi) \quad \dots (3)$$

This has the minimum value at zero at  $\phi = 0, \pm 2\pi/n, 4\pi/n$ , etc., and maxima at  $\phi = \pm \pi/n, 3\pi/n$ , etc. of  $U_0$ .

In less symmetrical molecules like 1,1,2-trisubstituted ethanes, separate expressions for each of the  $2\pi/6$  ranges are generally written as in Eq (4).

$$U(\phi) = U_1 - U_2 \cos n\phi \quad \dots (4)$$

Here,  $U_1$  and  $U_2$  may be adjusted in each of the six ranges to make the entire barrier continuous, and to make some rotamers more stable than other. However, in this case also, the potential minima correspond to perfectly staggered conformations.

Simpler linear function potentials are being employed in some cases<sup>13</sup>. Here  $U(\phi)$  is taken as a combination of linear functions of  $\phi$  in the various ranges such that the potential wells are V-shaped. Here also, minima are usually made to coincide with perfectly staggered geometry.

These pictures can explain apparent deviations of the order of 10-15°, when the potential barriers differ very much; however, they fail to account for 15-35° deviations observed. Also, the fact that  $J_+$  is experimentally found to increase with temperature (corresponding to a decrease in deviation at higher temperatures) discounts this model. (The model predicts the reverse). Thus, the actual minima must be displaced from normal positions.

Table 7—Deviations from Staggeredness, Calculated from Observed Coupling Constants in  $\text{Me}_3\text{C}-\text{CH}_2-\text{CHMe}-\text{CH}_2\text{Cl}$

Temp. (K)	$n_1$	$n_2$	$n_3$	$x$ (deg)	$y$ (deg)
380.9	0.585	0.365	0.050	27.2	17.2
360.8	0.594	0.361	0.045	28.2	17.7
339.9	0.605	0.357	0.039	29.5	15.8
319.2	0.616	0.351	0.033	29.6	17.8
301.9	0.626	0.345	0.028	30.7	17.5
282.3	0.639	0.338	0.023	32.1	16.8
261.5	0.653	0.329	0.018	33.4	15.9
242.0	0.668	0.318	0.014	34.3	15.2

$\Delta G$  (1) = 357 cal/mol;

$\Delta G$  (3) = 1857 cal/mol.

#### (iii) Effect of torsional vibrations on ensemble averaging

As can be readily seen, the situations described in the preceding section do not correspond to delta function potential wells. Temperature-dependent vibrational averaging do exist.

In cases where the potential barriers are high, the system approximates a simple harmonic oscillator; and when the barriers are low, the approximation is to a free rotor. In compounds under study, the potential barriers for internal rotation are of intermediate height and the overall solutions are intermediate between the two extreme approximations. However, the lower energy levels can be approximately represented by harmonic oscillator equations. These are the vibrational levels that are populated at the temperatures under study; and they correspond to the torsional vibrations of the molecule about the C—C bond. When temperature is increased, the higher energy levels are more populated. In a physical sense, amplitude of the torsional vibration increases at higher temperatures.

Now, if one considers a system with torsional vibrations, but devoid of rotational averaging, the measured coupling constants will be proportional to the ensembled averages of  $(\cos^2 \phi)$ 's. Any attempt to compute the dihedral angle from the observed  $J$  will provide only the arccos of the square-root of  $\langle \cos^2 \phi \rangle$ , which is not the same as  $\langle \phi \rangle$ .

We have made an attempt to estimate the influence of these enhanced torsional amplitude on the ensembled averages of  $\cos^2 \phi$ , and hence on the temperature-dependence of the coupling constants. An exact quantum mechanical calculation should weigh the values of  $\phi$  near the potential minima more heavily than would the calculation for the classical oscillator. However, the classical oscillator is a good enough model, for which

$$\langle \cos^2 \phi \rangle = \frac{1}{(2n+1)} \sum_{i=-n}^{i=+n} \cos^2(\phi + 0.1i) W(i) \quad \dots (5)$$

where  $n$  is the amplitude (in degrees) times 10.

The results summarized in Table 8 show that when the average amplitude of torsional oscillations increases from 30° at 240°K to about 40° at 380°K,  $J_+$  would increase only when the deviation from staggeredness is large, as indicated in this compound.

Thus, the increase in  $J_+$  corresponds to a new ensemble averaging of  $\cos^2 \phi$ , brought about by enhanced amplitude of torsional vibration. The apparent change in dihedral angle is, thus, not a physical reality; it is only a mathematical solution.

(iv) *Interaction between *t*-butyl and chlorine in  $\text{Me}_3\text{C}-\text{CH}_2-\text{CHMe}-\text{CH}_2\text{Cl}$*

(a) In this compound, the calculated dihedral angles showed considerable deviations from staggeredness (*vide supra*). However, the deviations are not identical in the two conformers, the *trans* form showing a greater deflection (Table 7). Thus the chloromethyl group approaches the *t*-butyl group more closely than does the methyl. Sheppard<sup>14</sup> has suggested that such a situation might result from intramolecular interaction.

(b) Conformational analysis about the  $\text{C}_2-\text{C}_3$  bond in this compound (Table 5) yielded a negative entropy for the equilibrium between rotamers I and II. Based on Mizushima's discussion<sup>4</sup> on the entropy difference between rotational isomers, no such entropy change can be anticipated in this compound, in the absence of intramolecular interaction. However, the entropy value of  $-0.539$  cal/deg/mol is too small to be used as a conclusive evidence.

(c) The above two indications prompted us to do a conformational analysis about the  $\text{C}_1-\text{C}_2$  bond in the compound (see Table 9). For purposes of comparison, the data for the corresponding alcohol are also summarized in Table 9.

The enthalpy difference between the conformers in which the chlorine is *trans* or *gauche* to the neopentyl group is 55 cal/mol. This value may be compared with the 178 cal/mol for the alcohol. The above difference may be attributed to some steric reasons. However, the entropy change in the chloro compound is  $-0.714$ , whereas it is only  $-0.276$  cal/deg/mol for the alcohol. It is not easy to explain this difference, without invoking an intramolecular interaction in the chloro compound.

(d) No accurate information about the *gauche-gauche* conformer is provided by the analysis. However, the following data provide some qualitative in-

Table 8—Effect of Increased Amplitude of Torsional Vibration on  $J_+$ , in Case of Distortion from Staggeredness

$n_1/n_2$	$x/y$ (deg)	Ampl (deg)	$J_a$ (Hz)	$J_b$ (Hz)	$J_+$ (Hz)
0.65/0.35	40/20	20	4.966	4.241	9.207
0.65/0.35	40/20	40	5.001	4.370	9.371
0.65/0.35	40/20	60	5.056	4.575	9.632
0.65/0.35	00/00	20	8.926	5.746	14.672
0.65/0.35	00/00	40	8.721	5.690	14.411
0.65/0.35	00/00	60	8.397	5.602	13.999

Table 9—Energy Difference between Conformers, about  $\text{C}_1-\text{C}_2$  Bond, in  $\text{Me}_3\text{C}-\text{CH}_2-\text{CHMe}-\text{CH}_2-\text{X}$

Equilibrium	X	$\Delta H$ (cal/mol)	$\Delta S$ (cal/deg/mol)
I $\rightleftharpoons$ II	Cl	55	-0.714
I $\rightleftharpoons$ II	OH	178	-0.276
I $\rightleftharpoons$ III	Cl	233	-0.850
I $\rightleftharpoons$ III	OH	1017	+2.03

formation, especially when used for comparative studies.

In the alcohol, conformers I and III (about  $\text{C}_1-\text{C}_2$  bond) differ by 1017 cal/mol; the difference in the corresponding chloride is only 233 cal/mol. Similarly, the entropy change for the equilibrium between I and III is  $+2.03$  in the alcohol and  $-0.85$  cal/deg/mol in the chloride. The indication is that the position of the chlorine between the neopentyl and methyl groups is not highly disfavoured.

The deduction from the conformational analysis about  $\text{C}_1-\text{C}_2$  bond, namely that chlorine interacts with methyl as well as neopentyl, is not surprising. Raman spectral<sup>15</sup>, microwave<sup>16</sup> and electron diffraction<sup>17</sup> studies have shown that the *gauche* form is the more stable form in *n*-propyl chloride; and an electrostatic attraction between the chlorine and the methyl has been proposed<sup>18</sup> to account for this.

Similarly, our finding that the rotamer in which the chlorine is flanked on either side by a methyl and a neopentyl is populated to the extent of 20-22% has also precedence in the literature. Thus electron diffraction studies have shown<sup>19</sup> a population of about 20% in the *gauche-gauche* conformation of isobutyl chloride.

The detection of a probable interaction between the chloromethyl and *t*-butyl groups is somewhat novel. It has been suggested<sup>20</sup> that the chlorine and methyl of *n*-butyl chloride attract each other, the pseudo five-membered ring conformer being populated to the extent of 24%. The population of the interacting forms is only 17.9-21.3% in our system. Of course, this does not necessarily mean that a pseudo

six-membered ring is less stable, since more steric repulsions are to be overcome in the *t*-butyl compound.

(v) *GIGO10, the modified computer program*

The  $\Delta S^\circ$  for the equilibrium conformers II and III is found to be very close to zero in all the twelve compounds having the general formula.  $R-C_6H_4-CH_2-CHMe-CH_2-R'$ . This is in spite of the fact that  $\Delta S^\circ$  and  $\Delta H^\circ$  values for the equilibria between conformers I and II, as well as between I and III, vary substantially in these compounds. Hence it seems appropriate to revise the program (GIGO5) to include the approximation that  $\Delta S^\circ$  between rotamers II and III is zero. This new program (GIGO10) is thus expected to handle more realistically cases like  $Me_3C-CH_2-CHMe-CH_2Cl$ , where large entropy differences between conformers II and III might result due to reasons other than intramolecular interaction. Conformational analysis about  $C_2-C_3$  bond of  $Me_3C-CH_2-CHMe-CH_2Cl$ , by GIGO10 is given in Table 10. This probably is more accurate than the  $\Delta H^\circ$  of 185 cal/mol and  $\Delta S^\circ$  of  $-0.539$  cal/deg/mol obtained by GIGO5.

Energy differences between conformers I and II in the twelve compounds,  $R-C_6H_4-CH_2-CHMe-CH_2-R'$ , are recalculated by GIGO10. These values are within 1% of the values calculated by GIGO5 (Table 3).

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Table 10—Conformational Analysis about  $C_2-C_3$  Bond of  $Me_3C-CH_2-CHMe-CH_2Cl$ , using GIGO10

Temp. (K)	$n_1$	$n_2$	$n_3$	$\Delta G$ (cal/mol)	$\Delta H$ (cal/mol)
380.9	0.597	0.354	0.049	396	157
360.8	0.603	0.353	0.044	383	156
339.9	0.604	0.357	0.039	356	143
319.2	0.620	0.347	0.033	369	168
301.9	0.625	0.346	0.028	355	165
282.3	0.629	0.347	0.024	333	155
261.5	0.634	0.346	0.019	315	151
242.0	0.646	0.339	0.015	309	157

$$\Delta H^\circ = 156 \pm 19 \text{ cal/mol;}$$

$$\Delta S^\circ = -0.628 \pm 0.065 \text{ cal/deg/mol.}$$

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# Photochemical Behaviour of $\beta$ -Ionol in Ether, Sodium Dodecyl Sulphate & *n*-Butyl Stearate Media

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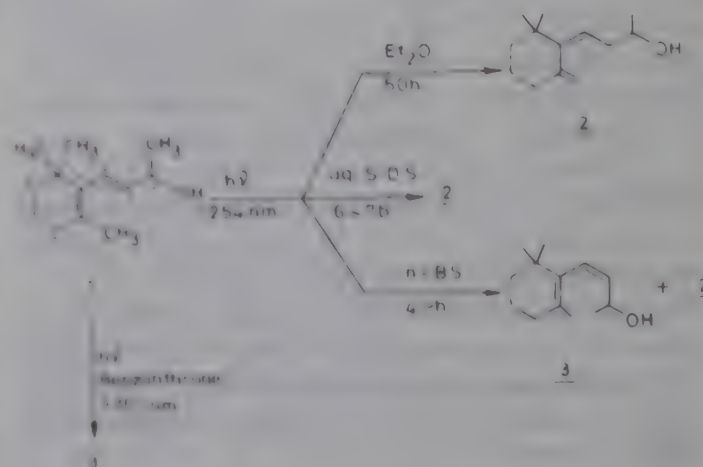
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Direct irradiation (254 nm) of *trans*- $\beta$ -ionol (**1**) either in diethyl ether or in aq. sodium dodecyl sulphate medium results in the formation of *retro*- $\gamma$ -ionol (**2**) due to 1,5-sigmatropic H-migration from the *trans*-isomer. Irradiation of **1**, entrapped in liquid crystalline medium of *n*-butyl stearate does not exhibit any photo-reaction. However, when **1** is irradiated in isotropic *n*-butyl stearate at 31°, *cis*-*trans* photoisomerization and 1,5-sigmatropic H-migration reactions are observed.

Linear polyenes in vitamin A series play important role as photoreceptors in many photobiological processes. For example, vitamin A aldehyde, present as prosthetic group in the membrane-bound pigments rhodopsins<sup>1,2</sup> is responsible for the photochemical properties of these pigments. In order to explain the excited state properties of these photoreceptors, extensive photochemical research has been undertaken on vitamin A and related polyenes<sup>3-6</sup>. Lower homologues in vitamin A series, such as  $\beta$ -ionyl compounds, have received considerable attention and used as model compounds to examine the effect of chain length and extended conjugation on the excited state characteristics of linear polyenes<sup>5</sup>. Since organized molecular assemblies have been argued to bear striking similarities to biological membranes<sup>7,8</sup> and have been found to control the rate and stereochemical course of photochemical reactions<sup>9-10</sup>, it was considered desirable to study the photobehaviour of linear polyenes in organized media. In the present investigation, a comparative examination of the photobehaviour of  $\beta$ -ionol (**1**) in isotropic solvent diethyl ether and in organized media of aqueous sodium dodecyl sulphate (SDS) micelle and *n*-butyl stearate (*n*-BS) liquid crystals has been made.

Excitations of  $\beta$ -ionyl compounds in organic solvents have earlier been shown to lead primarily to products arising by *cis*, *trans* photoisomerization and sigmatropic 1,5-hydrogen migration reactions<sup>5,11</sup>. Direct irradiation of an ethereal solution of **1** at 254 nm with a 16 watt low pressure Hg lamp for 50 hr resulted in the formation of > 80% of *retro*- $\gamma$ -ionol (**2**) (Scheme 1). Photolysis of SDS-micellized **1** under similar conditions for only 8 hr resulted in the formation of > 80% of *retro* product **2**. An action plot (Fig. 1) did not indicate the formation of any other photoproduct in the reaction. Compound **1**



SCHEME 1

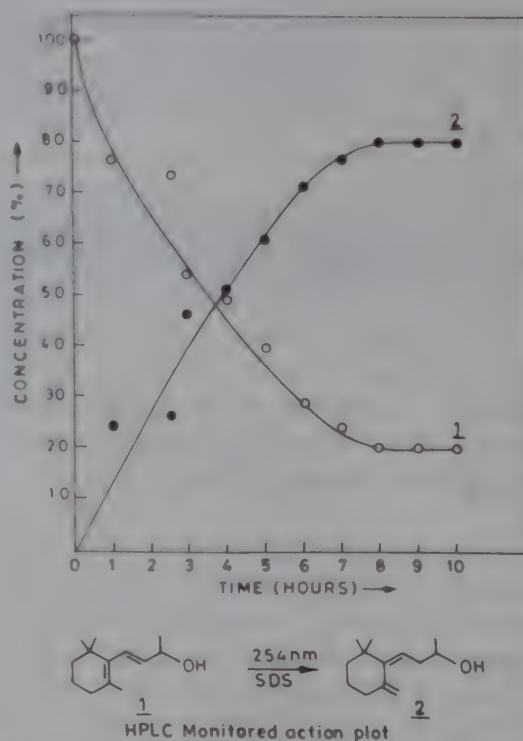


Fig. 1—HPLC monitored action plot for photolysis of **1** in aq. SDS

was found to be stable in SDS when kept for micellization for 12 hr in the dark, as evident by control experiments.

Irradiation of *n*-BS-incorporated **1** in the smectic phase with temperature in the range of 10–20° for 8 hr did not show any detectable reaction. However, irradiation in the isotropic phase at 31°C for 4 hr resulted in the formation of the *cis*-isomer **3** to the extent of 28%. Further irradiation of the samples for a prolonged period (< 20 hr) resulted in the formation of the *retro* product **2** in addition to **3**.

*retro*- $\gamma$ -Ionol (**2**), can arise from **1**, via a favoured sigmatropic 1,5-H shift in the cisoid diene system of **1**. Formation of *cis*- $\beta$ -ionol (**3**) was not detected during micellar photolysis indicating the formation of *retro* compound directly from *trans*-isomer. This observation is in agreement with previous studies<sup>12</sup> and supports the argument that the generation of 7-*cis* isomer (e.g. **3**) is not *a priori* requirement for the formation of *retro* products in the photochemistry of  $\beta$ -ionyl series of compounds.

It seems likely that  $\beta$ -ionol (**1**) gets oriented in the SDS micelle with its hydrophilic hydroxyl group protruding towards polar interface and trimethylcyclohexene unit aligned in the hydrophobic core (Fig. 2). Oxygen atom in the hydrophilic part of the substrate is expected to be involved in electrostatic interaction with counterion and in H-bonding with aqueous bulk phase of the micelle. This is expected to facilitate the availability of hydrogen of C<sub>6</sub>-CH<sub>3</sub> for migration to C-3. Preferred *S-cis* conformation<sup>13</sup> of the diene moiety of substrate makes C-3 ideally located for accepting the H atom released from C<sub>7</sub>-CH<sub>3</sub> in a sigmatropic process. That may be involved in an electrostatic interaction with polar region of the micelle gets support from a red shifted absorption band at 237 nm ( $\epsilon$ , 5388) in aqueous SDS as compared to a UV band at 233 nm ( $\epsilon$ , 5707) for **1** in methanol.

The photochemical properties of **1** are expected to be influenced by the orderly arrangement and viscosity of *n*-BS medium. In smectic phase, *n*-BS is characterized by a two dimensional structure with molecules packed in layers<sup>7</sup>. At temperatures below 20° *n*-BS tends to solidify, inhibiting the absorption of photons by sizeable amount of the substrate, and therefore, no detectable photochemical reaction could be observed when **1** was irradiated in the smectic phases (14°–20°) in *n*-BS medium. However, at temperature above 26° *n*-BS presents a viscous isotropic medium. Absorption of photons by **1** in *n*-BS at 31°, therefore, resulted in the observed photochemistry. The present observations on the photochemical behaviour of **1** entrapped in *n*-BS are a reflection of the relative ease of rotation around the

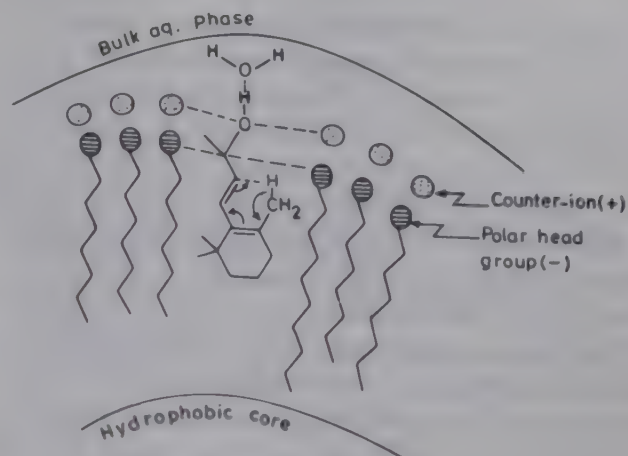


Fig. 2—Expected orientation of **1** in aq. SDS and 1,5-H shift at micellar interface

double bond in the planar excited state of  $\beta$ -ionyl compounds. It appears that medium-directed preferential decay of the planar excited state occurs because rotation to 90° species demands displacement of solvent molecules which present a large energy barrier if *n*-BS is the solvent. It has been suggested that the viscous-flow-solvent-cage-effect is added to influence the solute internal motion. Associated with this space requirement are the solvent-induced barriers for rotation of magnitude proportional to the number of solvent molecules to be displaced<sup>14,15</sup>. That the viscosity may influence the decay characteristics and overall molecular movements of excited  $\beta$ -ionol is supported by the fact that the rate of disappearance of  $\beta$ -ionol is significantly reduced when it is irradiated in a viscous isotropic medium such as paraffin oil. When  $\beta$ -ionol in 20% paraffin oil-hexane was irradiated for 2 min, the loss in the concentration of total  $\beta$ -ionol was ~ 12%. On the other hand, similar irradiation of  $\beta$ -ionol in highly viscous medium of paraffin oil resulted in ~ 1.5% loss in  $\beta$ -ionol concentration (Table 1). In fact, significant barrier to the configurational changes in **1**, in its excited state is imposed at ambient temperature when the photolysis is carried out even in 50% paraffin-hexane medium (Table 1). Therefore, the de-

Table 1—Influence of Viscosity of Solvent Media on Photochemical<sup>a</sup> Disappearance of  $\beta$ -Ionol (**1**)

Medium		$\eta$ (cp) <sup>25°</sup>	% Disappearance
% Paraffin	% Hexane		
20	80	0.506	11.7
50	50	5.626	2.37
70	30	22.397	2.13
100	—	—	1.48

<sup>a</sup>Irradiation at 25° in a 0.1 cm quartz cuvette for 2 min using 16 watt low pressure Hg lamp (254 nm; **1**,  $5.4 \times 10^{-4}$  M).

cay of excited states, responsible for configurational changes of **1** is greatly inhibited due to viscosity-dependent barrier. Prolonged irradiation of  $\beta$ -ionol (**1**) in *n*-BS resulted in 1,5-sigmatropic H shift which may be because of a relatively high electron density at C-3 in **1**. It is interesting to note that 1,5-H migration which is an efficient process in micellar system is suppressed by a competitive geometrical isomerization process in liquid crystalline medium. It has been noted<sup>5</sup> that extended conjugation and planarity in  $\beta$ -ionyl compounds induce geometrical isomerization process in competition to 1,5-H shift. It also appears that special requirement for molecular movement for 1,5-H shift in **1** is larger than the space required for double bond twist.

The present work shows that organized media can alter the photochemical reactivity of dienes in linear polyenes by interacting and orienting them in a defined order. It would be worth attempting to investigate the photobehaviour of longer polyenes in this series in molecular assemblies mimicking biological membrane.

## Experimental Procedure

### General

UV spectra were recorded on a Beckman DU-6 spectrophotometer, IR spectra on a Perkin-Elmer 625 IR spectrometer and PMR spectra on a Hitachi 600 (60 MHz) instrument using  $\text{CDCl}_3$  as solvent and TMS as an internal standard. HPLC analyses were performed on a Beckman 330 liquid chromatograph equipped with a Beckman model 160 wavelength selectable UV detector. Solvents were of AR grade, except petroleum ether, and used after distillation. Technical grade petroleum ether was purified and fractionated to obtain a fraction b.p. 62–65°. Sodium dodecyl sulphate and  $\beta$ -ionone were obtained from Aldrich Chemicals (USA) and used as received.  $\beta$ -Ionol (**1**) was prepared<sup>16</sup> in 83% yield by reducing  $\beta$ -ionone with sodium borohydride in methanol. *n*-Butyl stearate (*n*-BS) was synthesized by reacting stearic acid with *n*-butanol in the presence of boron trifluoride etherate<sup>17</sup>. *n*-Butyl stearate exhibited transition temperature of 14.8° (solid to smectic) and 26.3° (smectic to isotropic). Both, **1** and *n*-BS gave satisfactory analytical data which compared well with the data reported in literature. Per cent disappearance in **1** concentration during its photolysis in media of different viscosities was measured by monitoring absorbance with time in the reduction at 233 nm. Viscosities of hexane-paraffin oil systems were determined using an Ostwald viscometer following standard procedures.

### Photolysis

Irradiations were performed using a 16 watt low pressure Hg lamp (Applied Photophysics, APP model 3016; > 90%, 254 nm) housed in APP annular photoreactor model APQ 40.

Micellar solutions of  $\beta$ -ionol were prepared by stirring it in  $10^{-2}$  M solution of SDS in distilled water overnight in dark at ambient temperature. Clear, micellized solutions were taken in quartz tubes (int. diam., 10 mm), purged with  $\text{N}_2$  for 15 min, capped with rubber septum and sealed with parafilm. Liquid crystalline samples of **1** in *n*-BS were prepared by taking it (1% by weight) in *n*-BS in quartz vessel and purged with  $\text{N}_2$  for 15 min in the isotropic phase at about 35°, and sealed as described above. These samples were then photolyzed in the temperature-controlled reactor. Samples photolyzed in smectic phases were cooled slowly through the phase transition temperatures and allowed to equilibrate at the photolysis temperatures for 5–10 min. Progress of the reactions was monitored by HPLC. Irradiation in smectic phases of *n*-BS was carried out by taking samples in micro UV cells of 0.1 cm path-length.

### Photolysis of *trans*- $\beta$ -ionol (**1**) in SDS

Degassed and sealed sample of **1** (0.20 g) micellized in aq. SDS (50 ml) was irradiated for 9 hr. Progress of the reaction was monitored by HPLC (Zorbax ODS- $\text{C}_{18}$ , 250  $\times$  4.5 mm, MeOH, 0.7 ml/min, 236 nm). After photolysis the micelles were broken and photoproduct was taken up in ether. Usual work-up followed by flash column chromatography yielded of 4-(2',2'-dimethyl-6'-methylenecyclohexylidene)-butan-2-ol or *retro*- $\gamma$ -ionol (**2**) in 70% yield (140 mg); UV(MeOH): 214 nm ( $\epsilon$ , 4700); IR (neat): 3460, 3080, 900  $\text{cm}^{-1}$ ; PMR:  $\delta$  1.03 (6H, s,  $\text{C}_2$ - $\text{Me}_2$ ), 1.15 (3H, d,  $j$  = 6 Hz,  $\text{C}_2$ - $\text{CH}_3$ ), 1.35–1.60 (4H, m,  $\text{C}_3$ - $\text{H}_2$  and  $\text{C}_4$ - $\text{H}_2$ ), 2.0–2.7 (4H, m,  $\text{C}_3$ - $\text{H}_2$  &  $\text{C}_5$ - $\text{H}_2$ ); 3.0–3.7 (1H, m,  $\text{C}_2$ -H), 4.50 (1H, m,  $\text{C}-6' - \text{C} = \text{H}$ ), 4.90 (1H, bs,  $\text{C}_6 = \text{CH}$ ), 5.20 (1H, t,  $J$  = 6 Hz,  $\text{C}_4$ -H); HPLC  $R_f$  = 4.3 min.

### Photolysis of *trans*- $\beta$ -ionol (**1**) in *n*-butyl stearate

Degassed and sealed sample of **1** in *n*-BS was irradiated in the temperature range of 10–31°C. Photolysis at 31°C for 4 hr indicated the formation of *cis*- $\beta$ -ionol. Its characterization rested upon the comparison of HPLC  $R_f$  of authentic photolysis<sup>18</sup> of **2**. Prolonged irradiation for 20 hr resulted in the formation of 28% of **2** also.

### Acknowledgement

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## Absolute Stereochemistry of Cyclotagitinin-C

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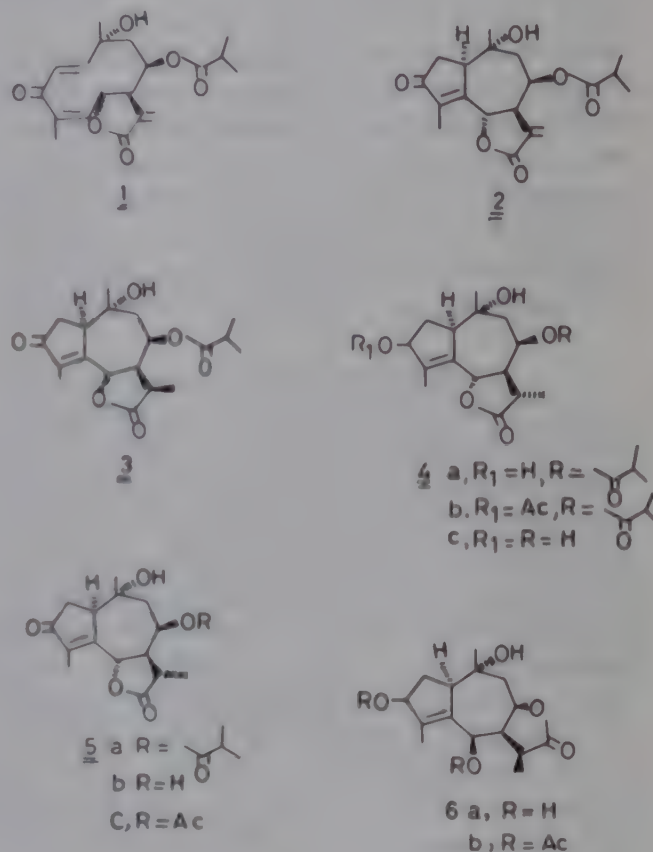
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Stereochemistry previously assigned to cyclotagitinin-C (**2**) obtained by acid-catalysed cyclization of tagitinin-C (**1**) has been confirmed through chemical correlation with 8-epi-isophotoartemisinic lactone acetate (**5c**). Compound (**5c**) is obtained from **2** via a series of reactions.

In an earlier article concerning transformation studies on tagitinin-C (**1**)—the major heliangolide sesquiterpene lactone of *Tithonia diversifolia*—it was reported that the acid-catalyzed cyclization of **1** provided cyclotagitinin-C (**2**)<sup>1</sup>. The stereochemistry assigned to the newly generated chiral centre at C-1 was based entirely on spectral data. We now present evidence which has unequivocally established that H-1 in **2** is indeed  $\alpha$ .

Hydrolysis of the ester side chain in **2** under acidic and basic conditions invariably yielded a complex mixture of products. Catalytic hydrogenation of **2** over 10% Pd/C furnished compound (**3**), m.p. 238–39°, in the PMR spectrum of which H-7 appeared as a broad doublet of doublets ( $J = 11, 5$  and  $8$  Hz) at  $\delta$  3.01 ( $J_{7,11} = 8$  Hz) suggestive of  $\beta$ -stereochemistry for C-11 methyl<sup>2</sup>. On the other hand sodium borohydride reduction of **2** furnished the diol (**4a**) wherein C-11 methyl was assigned the  $\alpha$ -stereochemistry on the basis of coupling constant between H-7 and H-11 ( $J_{7,11} = 13$  Hz). The diol (**4a**) on acetylation gave the monoacetate (**4b**), and on oxidation with  $MnO_2$  the  $\alpha,\beta$ -unsaturated ketone (**5a**), m.p. 217–19°. However, all attempts to hydrolyse **5a** with basic or acidic reagents led to extensive decomposition and yielded a complex mixture of products. Reaction of **4a** with sodium methoxide in methanol furnished two products (**4c**) and (**6a**), the formation of which was temperature dependent (see Experimental). In the PMR spectrum of **6a** signals due to isobutyrate group were absent and the proton under the lactone appeared as a doublet of doublets of doublet at  $\delta$  5.05 and H-6 appeared as a doublet at 4.64 ( $J = 4.5$  Hz), thus suggesting that the lactone ring in **6a** was fused to C-8 and C-6 hydroxyl and was  $\beta$ -oriented. Epimerization of alcohols under basic conditions is well documented<sup>3</sup>. Acetylation of **6a** furnished the acetate (**6b**) in the PMR spectrum of which H-6 appeared as a doublet at  $\delta$  5.94, indicative of its allylic nature.

Compound (**4c**) on oxidation with manganese di-



oxide furnished **5b** which was found to be contaminated with other minor products (PMR). Acetylation of **5b** followed by chromatographic purification led to pure **5c**, which was found to be identical with 8-epi-isophotoartemisinic lactone acetate<sup>4</sup>.

It is interesting to note that cyclotagitinin-C (**2**) has recently been found to co-occur with tagitinin-C (**1**) in *Greenmaniella resinosa*<sup>5</sup>.

### Experimental Procedure

Melting points were determined on a Kofler block and are uncorrected. IR spectra were recorded in  $CHCl_3$  on a Perkin Elmer 237B grating IR spectrophotometer and PMR spectra in  $CDCl_3$  on a Bruker HX-270 MHz instrument. Chemical shifts are

given in  $\delta$  ppm with TMS as an internal reference. Low and high resolution mass spectra were recorded on MS-30 and MS-902 instruments, respectively.

#### Hydrogenation of **2** : Formation of **3**

A solution of **2** (100 mg) in ethyl acetate (25 ml) was hydrogenated over Pd/C (10%, 100 mg) at atmospheric pressure for 15 min. Catalyst was filtered off and washed several times with ethyl acetate. The combined filtrate and washing was evaporated under reduced pressure and the residue purified by preparative TLC (EtOAc-pet. ether, 1:1) to yield **3** as a crystalline compound (70 mg), m.p. 138-39° (hexane-CHCl<sub>3</sub>); IR: 3600, 1775, 1730, 1700, 1625, 1140, 1000 and 935 cm<sup>-1</sup>; PMR: 3.37 (*m*, H-1), 2.61 (H-2a & 2b, centre of *AB* part of *ABX* system), 5.57 (*bd*, *J* = 12 Hz, H-6), 3.01 (*bdd*, *J* = 11.5 & 8 Hz, H-7), 5.50 (*bt*, *J* = 3.5 Hz, H-8), 2.37 (*dd*, *J* = 15 & 3.5 Hz, H-9a), 1.99 (*bdd*, *J* = 15 & 3.5 Hz, H-9b), 2.85 (*dq*, *J* = 8 & 7 Hz, H-11), 1.34 (*d*, *J* = 7 Hz, H-13), 1.03 (H-14), 1.97 (*t*, *J* = 1.5 Hz, H-15), 2.56 (*sept*, *J* = 7 Hz, H-2') and 1.21 (*d*, *J* = 7 Hz, H-3' and H-4'); <sup>13</sup>C NMR (CDCl<sub>3</sub>): 49.93 (*d*, C-1), 49.42 (*t*, C-2), 207.30 (*s*, C-3), 144.19 (*s*, C-4), 160.89 (*s*, C-5), 75.81 (*d*, C-6), 44.54 (*d*, C-7), 66.47 (*d*, C-8), 37.10 (*t*, C-9), 44.89 (*s*, C-10), 38.49 (*d*, C-11), 177.11 (*s*, C-12), 11.26 (*q*, C-13), 23.70 (*q*, C-15), 175.20 (*s*, C-1'), 34.35 (*d*, C-2') and 18.79 (*q*, C-3' and C-4'); MS:*m/z* (%) 350 (M<sup>+</sup>, 0.8), 280 (60), 262 (27.7) and 71 (100) (mol. wt found 350.1733. Calc C<sub>19</sub>H<sub>26</sub>O<sub>6</sub>: 350.1727).

#### Sodium borohydride reduction of **2** : Formation of **4a**

To a stirred solution of **2** (100 mg) in methanol (5 ml) at 5° sodium borohydride (100mg) was added in lots with TLC monitoring. The reaction mixture was diluted with water, acidified with dil acetic acid and extracted with chloroform. The extract was washed with water, dried (Na<sub>2</sub>SO<sub>4</sub>) and evaporated under reduced pressure. The residue after purification by preparative TLC (EtOAc-Bz, 1:1) yielded **4a** as a gum (70 mg); IR: 3550, 1775 and 1730 cm<sup>-1</sup>; PMR (C<sub>6</sub>D<sub>6</sub>): 2.47 (*bdd*, *J* = 8 & 6.5 Hz, H-1), 2.23 (*dt*, *J* = 14 & 8 Hz, H-2a), 1.5 (*dt*, *J* = 14 & 6.5 Hz, H-2b), 4.17 (*bdd*, *J* = 7 & 6.5 Hz, H-3), 4.95 (*bdd*, *J* = 11 & 2.5 Hz, H-6), 1.67 (*ddd*, *J* = 13, 11 & 1 Hz, H-7), 5.11 (*ddd*, *J* = 4, 3.5 & 1 Hz, H-8), 1.93 (*dd*, *J* = 15 & 3.5 Hz, H-9a), 1.25 (*bdd*, *J* = 15 & 4 Hz, H-9b), 2.10 (*dq*, *J* = 13 & 6.5 Hz, H-11), 1.04 (*d*, *J* = 6.5 Hz, H-13), 0.91 (H-14), 1.92 (*m*, H-15), 2.13 (*sept*, *J* = 7 Hz, H-2'), 0.91 (*d*, *J* = 7 Hz, H-3') and 0.90 (*d*, *J* = 7 Hz, H-4'); MS:*m/z* 352 (M<sup>+</sup>), 282, 264, 246, 228 and 71.

#### Acetylation of **4a** Formation of **4b**

Acetylation of **4a** (Ac<sub>2</sub>O/Py; overnight at room

temp), after work up and purification by preparative TLC (EtOAc-Bz, 1:4) furnished **4b** as a gum in quantitative yield; IR: 3600, 1775, 1730 and 1720 cm<sup>-1</sup>; PMR: 3.06 (*m*, H-1), 2.60 (H-2a), 1.74 (*dt*, *J* = 13 & 5 Hz, H-2b), 5.53 (*bt*, *J* = 5 Hz, H-3), 5.14 (*bd*, *J* = 9.5 Hz, H-6), 2.30 (H-7, H-9a and H-11), 5.37 (*t*, *J* = 4 Hz, H-8), 1.88 (H-9b), 1.26 (*d*, *J* = 6.5 Hz, H-13), 1.14 (H-14), 1.85 (*m*, H-15), 1.21 (*d*, *J* = 7 Hz, H-3' and H-4'), 2.10 (Ac); MS:*m/z* (%) (M<sup>+</sup>, 20) 334 (35), 316 (40), 306 (15), 164 (50), 246 (60), 228 (40) and 71 (100).

#### Manganese dioxide oxidation of **4a** : Formation of **5a**

To a stirred solution of **4a** (50 mg) in chloroform (3 ml) at room temperature was added excess of active MnO<sub>2</sub> with TLC monitoring. The reaction mixture was filtered and washed thoroughly with chloroform. On evaporation under reduced pressure it yielded a gum which on purification by preparative TLC (EtOAc-pet. ether, 1:1) yielded **5a** (35 mg), m.p. 217-19° (hexane-EtOAc); IR: 3500, 1775, 1725, 1700, 1625, 1125, 990, 950, 935 and 775 cm<sup>-1</sup>; PMR (C<sub>6</sub>D<sub>6</sub>): 2.30 (*m*, H-1), 2.25 (H-2a & H-2b), 4.89 (*dq*, *J* = 10.5 & 1.5 Hz, H-6), 1.67 (*ddd*, *J* = 12.5, 10.5 & 1.5 Hz, H-7), 5.06 (*dt*, *J* = 1.5 & 3.5 Hz, H-8), 1.81 (*dd*, *J* = 15 & 3.5 Hz, H-9a), 1.16 (*bdd*, *J* = 15 & 4 Hz, H-9b), 2.08 (*dq*, *J* = 12.5 & 7 Hz, H-11), 1.05 (*d*, *J* = 7 Hz, H-13), 0.57 (H-14), 2.00 (*t*, *J* = 1.5 Hz, H-15), 2.09 (*sept*, *J* = 7 Hz, H-2'), 0.87 (*d*, *J* = 7 Hz, H-3') and 0.89 (*d*, *J* = 7 Hz, H-4'); MS:*m/z* (%) 350 (2.8), 280 (8.4), 262 (23) and 71 (100); (Mol wt found 350.1729. Calc for C<sub>19</sub>H<sub>26</sub>O<sub>6</sub>: 350.1727).

#### Preparation of **6a** and **4c**

A solution of **4a** (50 mg) in dry methanol (2 ml) was treated with sodium methoxide solution (0.5 M, 0.5 ml) in methanol at 0° and the reaction mixture kept overnight at room temperature. It was diluted with cold water, acidified with dil acetic acid and extracted with chloroform and the organic extract dried (Na<sub>2</sub>SO<sub>4</sub>). Evaporation of solvent and complete removal of acetic acid by co-distillation with toluene followed by purification by preparative TLC (15% MeOH-CHCl<sub>3</sub>) furnished **6a** (30 mg) as the major product as a gum; IR: 3500, 1770, 1600, 1145 and 900 cm<sup>-1</sup>; PMR: 2.79 (*bdd*, *J* = 7.5 & 7 Hz, H-1), 2.40 (*dt*, *J* = 12.5 & 7.5 Hz, H-2a), 1.09 (*dt*, *J* = 12.5 & 7 Hz, H-2b), 4.39 (*bt*, *J* = 7 Hz, H-3), 4.64 (*d*, *J* = 4.5 Hz, H-6), 2.70 (*ddd*, *J* = 13, 7 & 4.5 Hz, H-7), 5.02 (*ddd*, *J* = 11.5, 7 & 5 Hz, H-8), 1.88 (*dd*, *J* = 13 & 11.5 Hz, H-9a), 1.79 (*dd*, *J* = 23 & 5 Hz, H-9b), 2.48 (*dd*, *J* = 13 & 7 Hz, H-11), 1.25 (*d*, *J* = 6.5 Hz, H-13), 1.19 (H-14) and 1.69 (*m*, H-15); MS:*m/z* (%) 282 (very weak), 264 (5.2), 246 (11.4), 178 (19.7),

156 (33) and 108 (100); MS (CI, isobutane): 283 (1.1), 265 (39.2) and 247 (100).

When the reaction mixture was kept at 5° for overnight **4c** was obtained as the major product as a gum (30 mg); IR: 3500, 1770, 1600, 1140 and 990  $\text{cm}^{-1}$ ; MS:  $m/z$  282 ( $\text{M}^+$ ), 264, 246, and 228. Due to poor solubility in  $\text{CDCl}_3$  satisfactory PMR spectrum of **4a** could not be recorded.

Acetylation of **6a** ( $\text{Ac}_2\text{O/Py}$ , overnight at room temp) gave the acetate **6b** as a crystalline solid, m.p. 176-77° ( $\text{EtOAc-hexane}$ ); IR: 3500, 1770, 1150, 1005, 990 and 955  $\text{cm}^{-1}$ ; PMR: 2.81 (*bdd*,  $J=7.5$  & 7 Hz, H-1), 2.63 (*dt*,  $J=12.5$  & 7.5 Hz, H-2a), 1.30 (H-2b), 5.50 (*br t*,  $J=7$  Hz, H-3), 5.94 (*d*,  $J=4.5$  Hz, H-6), 2.73 (*ddd*,  $J=13$ , 7 & 4.5 Hz, H-7), 5.05 (*ddd*,  $J=12$ , 7 & 4 Hz, H-8), 1.84 (*dd*,  $J=14$  & 12 Hz, H-9a), 1.02 (*bdd*,  $J=14$  & 4 Hz, H-9b), 2.40 (*dq*,  $J=13$  & 7 Hz, H-11), 1.37 (*d*,  $J=8.5$  Hz, H-13), 1.20 (H-14), 1.75 (*dd*,  $J=2$  & 1 Hz, H-15), 2.10 and 2.15 (Ac); MS:  $M/z$  (%) 264 ( $\text{M}^+-60-42$ , 12.5), 246 (68.3) and 228 (5.9).

#### Preparation of **5c**

Oxidation of **4c** (50 mg) with excess of active  $\text{MnO}_2$  as described earlier furnished **5b** (35 mg) which could not be made free of impurities and therefore was acetylated ( $\text{Ac}_2\text{O/Py}$ , overnight at

room temp). Usual work up and purification by preparative TLC (5%  $\text{MeOH-CHCl}_3$ ) furnished **5c** (25 mg) which was crystallised from ethyl acetate, m.p. 172-73°;  $[\alpha]_D + 72^\circ$  (reported<sup>4</sup> m.p. 174-75°,  $[\alpha]_D + 72^\circ$ ); IR: 3500, 1745, 1700, 1645, 1170, 995 and 945  $\text{cm}^{-1}$ ; PMR: 3.28 (*m*, H-1), 2.57 (H-2 centre of *AB* part of *ABX* system), 5.31 (*bd*,  $J=10.5$  Hz, H-6), 2.95 (*m*, H-7), 5.11 (*bt*,  $J=3.5$  Hz, H-8), 2.90 (*dd*,  $J=15$  & 3.5 Hz, H-9a), 1.99 (*bdd*,  $J=15$  & 4 Hz, H-9b), 2.45 (*m*, H-11), 1.30 (*d*,  $J=7$  Hz, H-13), 1.05 (H-14), 1.93 (*d*,  $J=2$  Hz, H-15) and 2.12 (Ac); MS:  $m/z$  322 ( $\text{M}^+$ ) 304, 280, 262 and 244.

#### Acknowledgement

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## Polynuclear Aromatic Hydrocarbons: Part XXVI—Acid-catalysed Rearrangement Through Spirocyclic Systems: Synthesis of 5,8-Dimethylphenanthro[1,2-*a*]anthracene

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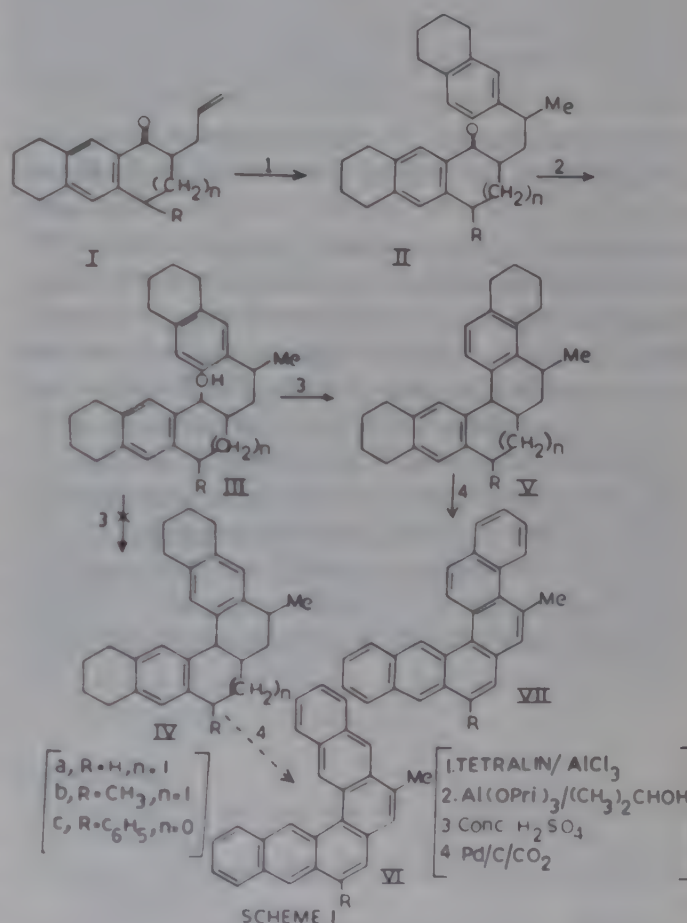
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Sulphuric acid-catalysed cyclisation of 1-hydroxy-4-methyl-2- $\beta$ -(6'-tetralyl)propyl]-1,2,3,4,5,6,7,8-octahydroanthracene (IIIb), obtained by Colonge-Mukherji cyclialkylation of tetralin with 2-allyl-4-methyl-1-oxo-1,2,3,4,5,6,7,8-octahydroanthracene (Ib) followed by Meerwein-Ponndorf-Verley reduction, affords 5,8-dimethyl-1,2,3,4,5,6,7,8,10,11,12,13,14b-tetradecahydrophenanthro[1,2-*a*]anthracene (Vb) presumably through the acid-catalysed rearrangement of the spirocyclic intermediate IX, instead of the desired 6,9-dimethyl-1,2,3,4,5,6,7,7a,8,9,11,12,13,14,15b-tetradecahydroanthra[1,2-*a*]anthracene (IVb). The compound Vb on dehydrogenation gives the title compound (VIIb).

Laarhoven and coworkers<sup>1</sup> have reported the synthesis of the parent anthra[1,2-*a*]anthracene through the photocyclodehydrogenation of appropriate 1,2-diarylethylene. Synthesis of 6-methylanthra[1,2-*a*]anthracene has been reported by us<sup>2</sup> earlier. In view of its highly symmetrical structure we became interested in the synthesis of 6,9-dimethylanthra[1,2-*a*]anthracene (VIb) through the sequence of Colonge-Mukherji cyclialkylation<sup>3</sup>, but to our dismay the reaction led to the formation of 5,8-dimethylphenanthro[1,2-*a*]anthracene (VIIb).

2-Allyl-4-methyl-1-oxo-1,2,3,4,5,6,7,8-octahydroanthracene<sup>4</sup> (Ib) was reacted with tetralin in the presence of anhyd. aluminium chloride at 0-5° and the resulting 4-methyl-1-oxo-2- $\beta$ -(6'-tetralyl)propyl]-1,2,3,4,5,6,7,8-octahydroanthracene (IIb; 56%) on reduction with aluminium isopropoxide<sup>5</sup> in refluxing isopropanol provided 1-hydroxy-4-methyl-2- $\beta$ -(6'-tetralyl)propyl]-1,2,3,4,5,6,7,8-octahydroanthracene (IIIb; Scheme 1) in a quantitative yield.

The alcohol IIIb on treatment with conc. sulphuric acid at 5-12° gave the hydroaromatic compound which was tentatively assigned the structure IVb which on dehydrogenation at 300-20° in the presence of 30% Pd/C in an atmosphere of carbon dioxide afforded a solid. It was thought to be 6,9-dimethylanthra[1,2-*a*]anthracene (VIb). However, its 100 MHz PMR spectrum did not conform to the suggested structure VIb as it exhibited two three-proton singlets at  $\delta$  2.88 and 3.23 thereby ruling out the structure VIb for the aromatised product and structure IVb for the hydroaromatic product. One would expect the two methyl groups at C-6 and C-9 in the highly symmetrical VIb to resonate as a six-proton singlet rather than two three-proton singlets at different fields. On the basis of PMR spectrum the aromatised product



could be assigned the structure 5,8-dimethylphenanthro[1,2-*a*]anthracene (VIIb). Thus, the two three-proton singlets at  $\delta$  2.88 and 3.23 may be assigned to the methyl protons at C-8 and C-9, respectively, the latter experiencing Van der Waals deshielding effect (Bay effect<sup>6</sup>). In the aromatic region, the one-proton singlet at  $\delta$  9.33, the one-proton doublet at 8.97, the one-proton doublet of a doublet at 8.86 and the one-proton singlet at 8.60 were assigned to H-14, H-15, H-4 and

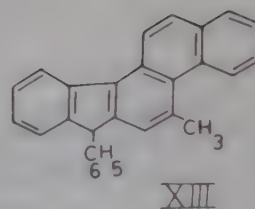
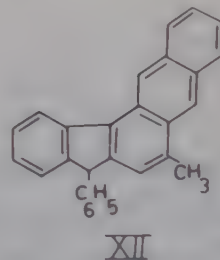
H-9, respectively. The ten-proton multiplet at  $\delta$  8.30-7.40 was assigned to the rest of the aromatic protons, thereby confirming the structure VIIb for the aromatised product and structure Vb for the hydroaromatic product.

The mass spectrum of VIIb exhibited the molecular ion at  $m/z$  356 (30%) followed by (M-1) peak at  $m/z$  355 which constituted the base peak, being stabilised as the tropylium ion having been formed after the loss of a hydrogen radical. The (M-15) peak at  $m/z$  341 (7%) resulted from the loss of a methyl radical.

In another set of reaction the temperature was controlled between 0-5° and the cyclised product aromatised by heating with Pd/C at 300-320° in an atmosphere of carbon dioxide. The aromatised product was found to be an intractable mixture of VIb and VIIb (and hence IVb and Vb) in the ratio of 5:2 determined on the basis of integration of the two methyl signals at  $\delta$  2.88 and 3.23. We were unable to procure pure VIb from the mixture. Attempts effecting cyclisation at still lower temperatures were unsuccessful due to pre-solidification of the alcohol III at these temperatures.

Rationale for the above abnormality could be provided from Newman's observation<sup>7</sup> that during cyclisation spirocyclic products are formed at higher temperatures, which undergo rearrangement in the acidic media providing the rearranged products. Thus, in analogy with the Newman's observations<sup>1</sup> a mechanism (Scheme 2) could be suggested for the observed rearrangement. Cleavage of bond-a in IX would lead to the normal product IVb while that of bond-b in IX to the rearranged product Vb through X and XI.

In order to determine the generality of the phenomenon, 1-hydroxy-2-[ $\beta$ -(6'-tetralyl)propyl]-1,2,3,4,5,6,7,8-octahydroanthracene (IIIa)<sup>2</sup> was also subjected to cyclisation with conc.  $H_2SO_4$  between 5° and 12° and the cyclised product dehydrogenated with Pd/C



at 300-320° in an atmosphere of carbon dioxide. The 100 MHz PMR spectrum of the mixture exhibited two singlets at  $\delta$  3.16 and 2.83 in the ratio of 1:1. The former obviously belonged to the rearranged product (VIIa) whereas the latter belonged to the normal product (VIa)<sup>2</sup>.

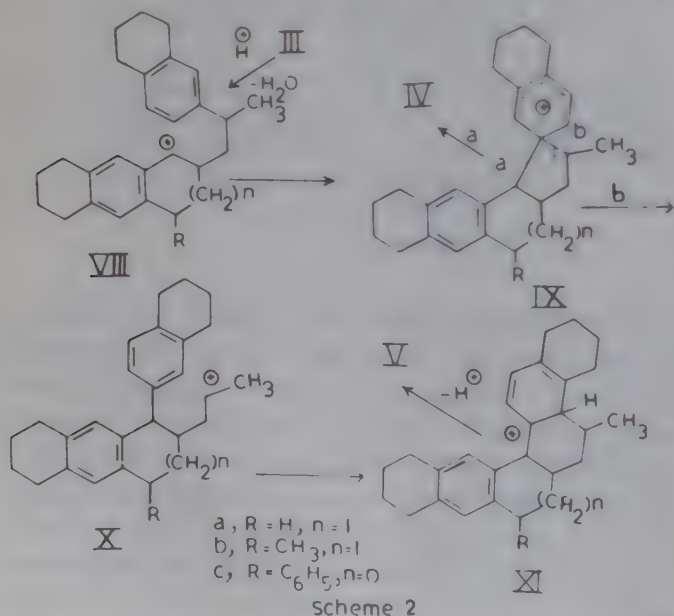
Similarly, during cyclisation<sup>8</sup> 2-[ $\beta$ -(6'-tetralyl)propyl]-3-phenyl-1-ol-indane (IIIc) underwent partial rearrangement to give a mixture of cyclised products (IVc and Vc) which on aromatisation with Pd/C at 300-320° in an atmosphere of  $CO_2$  gave a mixture of 8H-6-methyl-8-phenylindeno[1,2-a]anthracene (XII) and 7H-5-methyl-7-phenylindeno[1,2-a]phenanthrene (XIII) in the ratio of 1:2 as evidenced by the appearance of two singlets (due to methyl protons) at  $\delta$  2.81 and 3.11 in the ratio of 1:2 in its PMR spectrum. Similarly, the singlets appearing at  $\delta$  5.04 and 5.12 due to aliphatic protons were also in the ratio of 1:2.

### Experimental Procedure

M.ps and b.ps are uncorrected. IR spectra were run on a Beckman IR-20 spectrophotometer ( $\nu$  max in  $cm^{-1}$ ) and PMR spectra on a Varian AD 100 spectrometer using TMS as internal reference (chemical shifts in  $\delta$ -scale). Silica gel was used for both TLC and column chromatography. Pet. ether of boiling range 60-80° was used. Extinction coefficients are given in parenthesis as log  $\epsilon$ .

#### 4-Methyl-1-oxo-2-[ $\beta$ -(6'-tetralyl)propyl]1,2,3,4,5,6,7,8-octahydroanthracene (IIb)

2-Allyl-4-methyl-1-oxo-1,2,3,4,5,6,7,8-octahydroanthracene (Ib; 4.8 g) was subjected to anhyd. aluminium chloride (6.0 g) catalysed reaction with freshly distilled tetralin (45 ml) at 0-5° by gradual alternate addition of aluminium chloride and the ketone I according to the conditions described by Sharma *et al.*<sup>1</sup>. The reaction product was poured into ice-HCl and the organic material taken up in ether, washed till free from acidic impurities and dried ( $MgSO_4$ ). Removal of solvent and distillation of the residue under reduced pressure gave 4.1 g (56.2%) of IIb, b.p. 235-40°/2mm (Found: C, 86.8; H, 8.4.  $C_{28}H_{34}O$  requires C, 86.99; H, 8.86%).  $R_f$  0.54 (benzene), IR(neat): 1680 ( $C=O$ ). Its 2,4-DNP derivative was prepared as usual which on crystallisation from benzene melted at 102-3° (Found: N, 9.6.  $C_{34}H_{38}O_4N_4$  requires N, 9.92%).



*1-Hydroxy-4-methyl-2-[β-(6'-tetralyl)propyl]-1,2,3,4,5,6,7,8-octahydroanthracene (IIIb)*

The ketone IIb (3.6g) in dry isopropanol (50 ml) was smoothly reduced with aluminium isopropoxide (from 2.5 g of aluminium) by the usual method<sup>5</sup>. When the distillate became acetone free (ca, 10hr), the reaction mixture was poured onto crushed ice containing ammonium chloride solution, and the organic material taken up in ether, washed with water and dried (Na<sub>2</sub>SO<sub>4</sub>). Removal of solvent gave 3.3g (91.1%) of the carbinol (IIIb), b.p 230-35°/5 mm; IR (neat): 3420-3380 (OH).

*5,8-Dimethyl-1,2,3,4,5,6,6a,7,8,10,11,12,13,14b-tetra-decahydrophenanthra[1,2-a]anthracene (Vb)*

The carbinol IIIb (1.7g) was treated with conc. sulphuric and (3 ml, d 1.84) at 5-12° for 4 hr. The reaction mixture was poured into ice-water, and the organic material extracted with ether, washed till free from acid and dried (Na<sub>2</sub>SO<sub>4</sub>). Removal of solvent followed by column chromatography of the residue on silica gel using pet. ether as eluant afforded 1.1 g (67.6%) of Vb (Found: C, 90.6; H, 8.9. C<sub>28</sub>H<sub>34</sub> requires C, 90.75; H, 9.24); R<sub>f</sub> 0.6 (benzene-pet ether; 1:1).

*5,8-Dimethylphenanthro [1,2-a]anthracene (VIIb)*

The hydroaromatic compound Vb (1.0g) was dehydrogenated with 30% Pd/C (0.16g) at 300-320° for 4 hr in a current of carbon dioxide. The organic material was extracted with hot chloroform, filtered hot and the solvent removed. The residue was dissolved in benzene and passed through a column of silica gel and eluted with pet. ether to afford 0.6g (62.3%) of VIIb which on crystallisation from benzene melted at 215-16° (Found: C 94.2; H, 5.8. C<sub>28</sub>H<sub>20</sub> requires C, 94.34; H, 5.65%); R<sub>f</sub> 0.6 (benzene-pet. ether; 1:1); UV(ethanol): 231 (log<sub>e</sub> 5.21), 242(5.42), 288(4.84), 300(5.09), 312(5.43), 330(5.05), 356(4.92), 410(4.07) and 420nm (4.20).

*6,9-Dimethylantra [1,2-a]anthracene (VIb) and 5,8-dimethyl-phenanthra [1,2-a]anthracene (VIIb)*

The carbinol IIIb (1.2g) was treated with conc. sulphuric acid (2ml, d 1.84) at 0-5° for 4 hr. The reaction mixture was poured into ice-HCl, and extracted with ether. The extract was washed till free from acid, dried (Na<sub>2</sub>SO<sub>4</sub>), solvent removed and the residue column chromatographed using pet. ether as eluant to afford 0.92 g (80.4%) of the cyclised compounds (IVb and Vb).

The mixture of hydroaromatic compounds (IVb and Vb; 0.86 g) was heated with 30% Pd/C (0.15g) at 300-320° for 4 hr in current of carbon dioxide, and extracted with hot chloroform. Removal of the solvent provided 0.50 g (60.5%) of a solid, m.p. 202-6° (Found: C, 94.1; H, 5.8. C<sub>28</sub>H<sub>20</sub> requires C, 94.34%; H,

5.66%); PMR (CDCl<sub>3</sub>): δ 9.66 (s, H-15 and H-16 of VIb), 8.60 (s, H-5 and H-10 of VIb), 9.26 (s, H-14 of VIIb), 8.91 (d, H-15 of VIIb), 8.80 (dd, H-4 of VIIb), 8.55 (s, H-9 of VIIb), 8.27-7.37 (remaining aromatic protons of VIb and VIIb), 3.17 (s, C<sub>5</sub>-CH<sub>3</sub> of VIIb), 2.88 (s, C<sub>8</sub>-CH<sub>3</sub> of VIIb), 2.83 (s, C<sub>6</sub>-CH<sub>3</sub> and C<sub>9</sub>-CH<sub>3</sub> of VIb).

*6-Methylantra [1,2-a]anthracene (VIa) and 5-Methylphenanthra [1,2-a]anthracene (VIIa)*

The carbinol IIIa (2.3 g) was treated with conc. H<sub>2</sub>SO<sub>4</sub> (3.6 ml, d 1.84) at 5-12° for 4 hr. Usual work-up of the reaction mixture provided 1.7 g (77.6%) of IVa and Va which (1.4g) on dehydrogenation with 30% Pd/C (0.35g) at 300-20° in the usual manner provided 0.9 g (66.9%) of the products (VIa + VIIa), m.p. 177-81°; PMR (CDCl<sub>3</sub>): δ 9.70 (s, H-15 of VIa), 9.63 (s, H-16 of VIa), 8.59 (s, H-5 of VIa), 8.43 (s, H-10 of VIa), 9.26 (s, H-14 of VIIa), 8.97 (d, H-15 of VIIa), 8.78 (dd, H-14 of VIIa), 8.37 (s, H-9 of VIIa), 2.83 (s, C<sub>6</sub>-Me of VIa), 3.11 (s, C<sub>5</sub>Me of VIIa) and 8.30-7.41 (remaining aromatic protons).

*8H-6-Methyl-8-phenylindeno [1,2-a]anthracene (XII) and 7H-5-Methyl-7-phenylindeno [1,2-a]phenanthrene (XIII)*

1-Hydroxy-3-phenyl-2-[β-(6'-tetralyl)propyl]indane<sup>8</sup> (1.1g) was treated with conc. sulphuric acid (2ml, d 1.84) at 0-5° and the contents were mixed intimately when the temperature went upto 10°. Usual work-up provided 0.85g (81.1%) of a viscous oil (VIc and Vc).

The mixture (Vc + VIc) was dehydrogenated by heating with 30% Pd/C for 4 hr in an atmosphere of carbon dioxide at 300-320°. Usual work-up and column chromatography (silica gel) gave 0.45 g (57.5%) of the solid, m.p. 170-75° (Found: C, 93.9; H, 6.0. C<sub>28</sub>H<sub>20</sub> requires C, 94.3, H, 5.7%); R<sub>f</sub> 0.56 (benzene); PMR (CDCl<sub>3</sub>): δ 2.81 (s, C<sub>6</sub>-CH<sub>3</sub> of XII), 3.11 (s, C<sub>5</sub>-CH<sub>3</sub> of XIII), 5.04 (s, H-8 of XII), 5.12 (s, H-7 of XIII), 7.00 to 8.5 (all the aromatic protons).

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## Total Synthesis of Heterocyclic Steroids : Part IX—Synthesis of ( $\pm$ )-8-Aza-3-thia-A-nor-9 $\beta$ , 14 $\alpha$ -estra-1, 5(10)-dien-12-one & Its 14 $\beta$ -Isomer<sup>††</sup>

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Total synthesis of ( $\pm$ )-8-aza-3-thia-A-nor-9 $\beta$ , 14 $\alpha$ -estra-1, 5(10)-dien-12-one (IX) and its 14  $\beta$ -isomer (XII) has been achieved starting from 2-(2-thienyl) ethylamine (I) as an A-ring precursor and cyclopentanone (VI) as D-ring moiety. The amine (I) is condensed with diethyl malonate (II) to give ethyl N-2-(2-thienylethyl)-malonamate (III). The amide ester (III) on cyclisation under Bischler-Napieralski-reaction conditions yields 1-carbethoxymethylene-1H, 4H-2,3-dihydrothieno[3,2-c]pyridine (IV). The bicyclic ester (IV) on catalytic hydrogenation furnishes 1-carbethoxymethyl-1,2,3,4-tetrahydrothieno [3,2-c]pyridine (V). The ester (V) on condensation with cyclopentanone (VI) under acidic conditions yields 8-aza-3-thia-A-norestra-1, 5(10), 13-trien-12-one (VII), which on treatment with excess of methyl iodide gives a mixture of 11a-methyl-1, 2, 5, 6, 9b, 10-hexahydro-thieno-3H,11-oxo3H, 11H-thieno[3,2-c]cyclopentano[7]quinolizinium iodide (VIII) and C-methylated compound (IX). The quinolizinium salt (VIII) is reduced with lithium aluminium hydride to give a mixture of four isomers of 8-aza-3-thia-A-norestra-1, 5-(10)-dien-12-ol (X). The mixture of alcohols (X) on Jones' oxidation gives a mixture of 8-aza-3-thia-A-nor-9  $\beta$ , 14 $\alpha$ -estra-1, 5-(10)-dien-12-one (XI) and 8-aza-3-thia-A-nor-9 $\beta$ , 14 $\beta$ -estra-1, 5-(10)-dien-12-one (XII).

Replacement of a carbon of the steroidal skeleton by nitrogen results in the formation of several azasteroids possessing various biological activities<sup>1-3</sup> such as antiviral<sup>1</sup>, local anaesthetic<sup>2</sup>, anti-inflammatory<sup>3</sup>, anti-cancer<sup>4</sup>, etc.

In the earlier two parts of this series, the synthesis of 8, 13-diazasteroids with modification in the A-ring has been reported<sup>6</sup>. A literature survey revealed that although several modified 8-azasteroids were known, there was no report on the synthesis of 8-azasteroid having a sulphur atom in the A-ring. Replacement of the A-benzenoid ring of 8-azaestrone molecule with a heteroaromatic ring such as thiophene ring, and the effect of a sulphur atom in the A-ring on the biological activities of the resulting compound have now been studied.

An attempt to synthesise-( $\pm$ )-8-aza-3-thia-A-norestra-1, 5(10)-dien-17-one following the route of Brown *et al.*<sup>7</sup> was unsuccessful. The synthesis of isomeric 8-aza-3-thia-A-norestra-1, 5(10)-diene-12-ones (XI) and (XII) was achieved by the method of Reine and Mayers<sup>8</sup>.

2-(2-Thienyl)ethylamine<sup>9</sup> (I) was condensed with diethyl malonate (II) at 125-30° to give ethyl N-2-(2-thienylethyl)malonamate (III). The amide (III) was cyclised by refluxing it in toluene using phosphorus pentoxide to afford 1-carbethoxymethylene-1H, 4H-2, 3-dihydrothieno[3,2-c]pyridine (IV) in 79% yi-

eld. Its UV spectrum (methanol) showed bands at 324 and 218 nm with high  $\epsilon$  values ( $> N-C=C-CO$  chromophore)<sup>10</sup>. The IR spectrum of IV showed bands at 3333 (NH), 1645 (conjugated ester gr.) and 1605  $cm^{-1}$  ( $\beta$ -amino- $\alpha$ ,  $\beta$ -unsaturated group)<sup>11</sup>. The band at 1661  $cm^{-1}$  (amide C=O) was absent indicating the involvement of the amide carbonyl group during cyclisation. The appearance of signals at  $\delta$  4.94 (vinyl proton) and 8.63 (NH) in the PMR spectrum (carbon tetrachloride) established the exo-double bond in the resultant compound (IV). The catalytic hydrogenation of the unsaturated amino ester (IV) over platinum oxide provided 1-carbethoxymethyl-1, 2,3,4-tetrahydrothieno[3,2-c]pyridine (V) in 76% yield. The completion of hydrogenation was evident from UV spectrum (methanol). It showed an absorption maximum at 232 nm (substituted thiophenic system). The IR spectrum showed bands at 3356 (NH), 1724  $cm^{-1}$  (ester C=O). The band at 1605  $cm^{-1}$  ( $\beta$ -amino- $\alpha$ ,  $\beta$ -unsaturated group) was absent. The signals at  $\delta$  2.28 (NH), 6.73 and 7.02 (thiophene protons) were discernible in the PMR spectrum in carbon tetrachloride.

The usual tetracyclic compound 8-aza-3-thia-A-norestra-1, 5(10), 13-trien-12-one (VII) was obtained in 68% yield when V was condensed with cyclopentanone (VI) in the presence of trifluoroacetic acid. Its UV spectrum (methanol) showed absorption maxima at 232 and 239 nm with high  $\epsilon$  values ( $> N-C=C-CO$  chromophore)<sup>10</sup>. It showed strong bands at 1626 and 1575  $cm^{-1}$  ( $\beta$ -amino- $\alpha$ ,  $\beta$ -unsaturated ketone) in the IR spectrum (KBr)<sup>11</sup>. The PMR spectrum ( $CDCl_3$ )

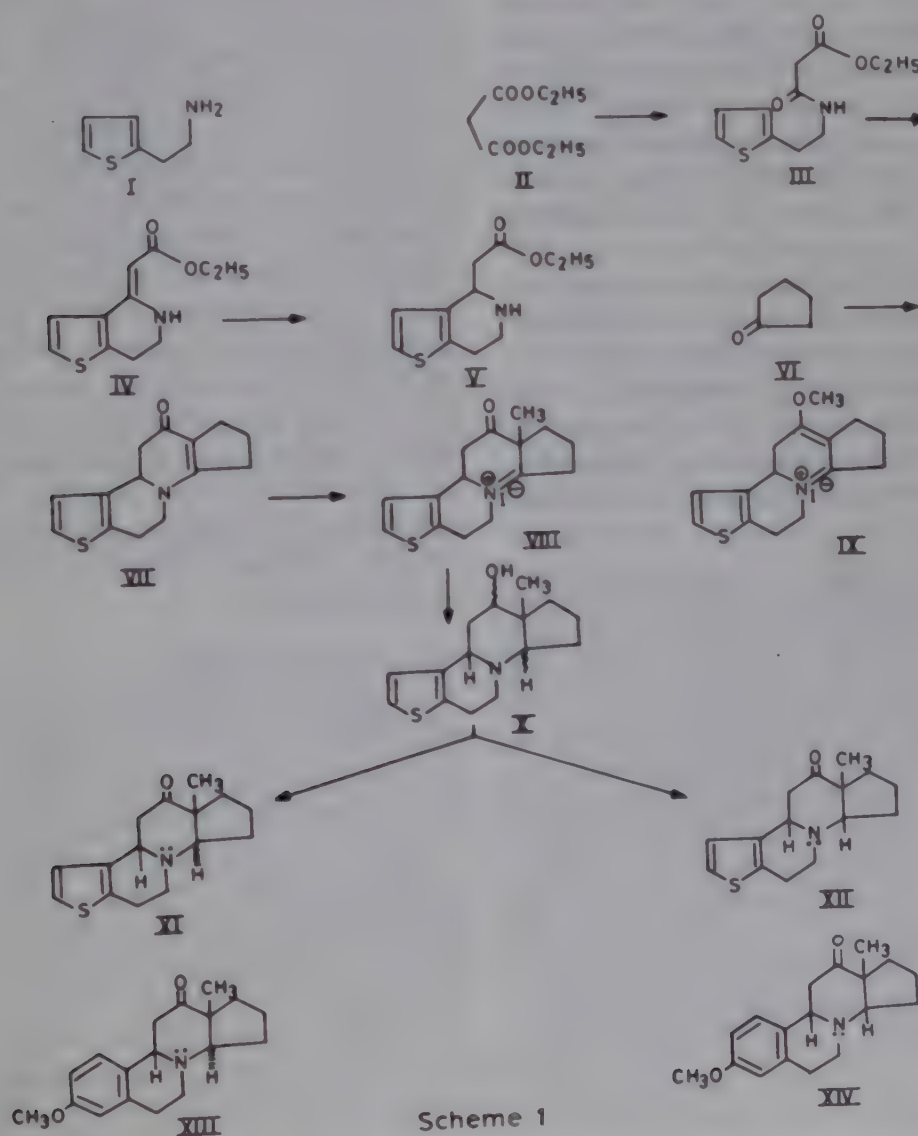
<sup>†</sup>This paper forms a part of the Ph D thesis of S H T submitted to the University of Bombay in 1982.

<sup>††</sup>All the compounds in the synthetic sequence are racemic. To clarify the stereochemical presentation only one isomer is depicted.

showed signals at  $\delta$  4.65 (C-9 proton), 6.89 and 7.23 (thiophene protons). The position of the double bond between C-13 and C-14 was established by the absence of a signal due to vinyl proton in the olefinic region. The introduction of the angular methyl group at C-13 was achieved by treatment of the enaminoketone (VIII) with excess of methyl iodide, when a mixture of C-methylated (VIII) and O-methylated (IX) salts was obtained in 88% yield. The UV spectrum (methanol) showed absorption maxima at 330 ( $>\text{N}=\text{C}-\text{C}=\text{C}-\text{OCH}_3$  chromophore) corresponding to the O-methylated salt (IX) and at 220 nm (substituted thiophene system). Fractional crystallisation of the mixture from acetonitrile gave pure 11a-methyl-1,2,5,6,9b,10-hexahydro-11-oxo-3H,11H-thieno [3,2-a] cyclopentano[f] quinolizinium iodide (VIII) in 77.5% yield. Its UV spectrum (methanol) showed absorption maximum at 220 nm (substituted thiophenic system). The bands at 1730 ( $\text{C}=\text{O}$ ) and 1667  $\text{cm}^{-1}$  ( $-\text{C}=\text{N}^+$ ) were observed in the IR spectrum (KBr). The PMR spectrum (trifluoroacetic acid) showed signals at  $\delta$  1.77 (C-13  $\text{CH}_3$ ), 6.0 (C-9 proton), 6.96 and 7.43 (thiophene

protons). The quinolizinium salt (VIII) was reduced with lithium aluminium hydride in refluxing tetrahydrofuran to give a mixture of four isomeric alcohols (X). The IR spectrum of the crude product showed a band at 3448  $\text{cm}^{-1}$  (OH), whereas the band at 1730  $\text{cm}^{-1}$  ( $\text{C}=\text{O}$ ) was absent. The crude mixture thus obtained was subjected to Jones' oxidation without further purification to give a mixture of 8-aza-3-thia-A-nor-9 $\beta$ ,14 $\alpha$ -estra-1,5(10)-dien-12-one (XI) and the corresponding 14 $\beta$ -isomer (XII) (Scheme 1) in 26% and 34.2% yields, respectively. The stereoisomer XI showed the UV absorption maximum at 236 nm (substituted thiophenic system). Its IR spectrum (KBr) displayed a simple absorption in the C-H stretching vibration region (absence of Bohlmann bands)<sup>12</sup> and a band at 1718  $\text{cm}^{-1}$  ( $\text{C}=\text{O}$ ). The signals at  $\delta$  1.22 (C-13  $\text{CH}_3$ ), 4.7 (C-9 proton), 6.91 and 7.14 (thiophene protons) were observed in the PMR spectrum ( $\text{CDCl}_3$ ) of XI.

The UV spectrum (methanol) of the other isomer (XII) exhibited an absorption maximum at 232 nm (substituted thiophenic system). It showed clear bands



Scheme 1

at 2874, 2833 (Bohlmann bands)<sup>12</sup> and 1701  $\text{cm}^{-1}$  (C=O) in the IR spectrum (KBr). The PMR spectrum ( $\text{CDCl}_3$ ) showed signals at  $\delta$  1.2 (C-13  $\text{CH}_3$ ), 3.88 (C-9 proton), 6.76 and 7.17 (thiophene protons).

The B/C ring stereochemistry of both the stereoisomers (XI) and (XII) was established on the basis of IR and PMR spectral data. The absence of Bohlmann bands and the downfield shift at  $\delta$  4.7 for the C-9 proton, established the *cis*-quinolizidine type structure for the B/C ring junction in the stereoisomer XI. Similarly, the presence of Bohlmann bands at 2874 and 2833  $\text{cm}^{-1}$  in the IR spectrum and the chemical shift at  $\delta$  3.88 for the C-9 proton, indicated the *trans*-quinolizidine type structure for the B/C ring junction in the stereoisomer XII.

The C/D ring stereochemistry was further established in both the stereoisomers XI and XII by analogy with the work done by Brown and co-workers<sup>13</sup> on the stereochemical assignment of 3-methoxy-8-azaestra-1, 3, 5(10)-trien-12-one (XIII) and its 14 $\beta$ -isomer (XIV). The overall configuration for the isomer XV was assigned as *cis-syn-trans* on the basis of single crystal X-ray analysis<sup>14</sup>. The upfield shift for the C-13 methyl protons from  $\delta$  1.2 to 1.1 was observed in the PMR spectrum of XV on changing the solvent from deuteriochloroform to benzene. This observation was consistent with a similar upfield shift for the axially oriented C-13 methyl group  $\alpha$  to the carbonyl group in the case of the corresponding carbocyclic steroid as reported by Bhacca and Williams<sup>15</sup>. Although, it was reported by Brown *et al.* that the Bhacca and Williams correlation is not always dependable in the case of 8-azasteroids, as the chemical shift of the methyl group is subjected to the anisotropic effect of the electron pair of nitrogen at C-8, the single crystal X-ray analysis of the stereoisomer (XIII) confirmed the axial orientation for the C-13 methyl group.

The stereochemistry of the C/D ring junction in the stereoisomer XI was assigned as *trans* by analogy with the results obtained for the stereoisomer XIII. The stereoisomer XI showed an upfield shift for the C-13 methyl protons from  $\delta$  1.22 in deuteriochloroform to 1.05 in benzene. Thus, it could be concluded by analogy that the C-13 methyl group was also axially oriented. Further, the same reaction sequence as used by Reine and Meyers for the synthesis of the stereoisomer XIV was employed for the synthesis of the A-thieno-8-azasteroid (XI). It could reasonably be concluded that the reaction followed the same pathways leading to the same stereochemistry of the C/D ring junction in the compound XI. Furthermore, the chemical shifts for the C-9 and C-18 protons of this isomer were fairly comparable with those of the isomer

XIII having *cis-syn-trans* configuration as reported by Brown *et al.* (Table 1). Hence, the overall configuration could be assigned as *cis-syn-trans* for the stereoisomer XI. Therefore, the structure of XI could be assigned as 8-aza-3-thia-A-nor-9 $\beta$ , 14  $\alpha$ -estra-1, 5-(10)-dien-12-one. The IR and PMR spectral data of the isomers XI and XII are given in Table 1 for comparison.

The stereochemistry of C/D ring junction in the stereoisomer XII was established by comparison of its spectral data with those reported by Brown *et al.* for the isomer XIV (Table 1). The configuration of the stereoisomer XIV was assigned as *trans-syn-cis*. Though, there was an upfield shift from  $\delta$  1.22 in deuteriochloroform to 1.04 in benzene for the C-13 methyl protons in the PMR spectrum of XIV, it was found to be equatorially oriented by single crystal X-ray analysis. Thus, the Bhacca-Williams correlation was not applicable in the case of the isomer XIV.

The stereoisomer XII also showed an upfield shift for C-13 methyl protons in the PMR spectrum from  $\delta$  1.2 in deuteriochloroform to 1.05 in benzene. Though, there was an upfield shift, the inapplicability of the Bhacca-Williams correlation could be expected as in the case of the stereoisomer XIV for the equatorially oriented C-13 methyl protons. The isomer XII was prepared by the same sequence of reactions as reported by Reine and Meyers for the stereoisomer XIV. Hence, it could be concluded that the reaction followed the same pathways leading to the same stereochemistry of the C/D ring junction in the compound XII. Further, the spectral data of the isomer XII were fairly comparable (Table 1) with those of the stereoisomer XIV having *trans-syn-cis* configuration. Therefore, it could be concluded that the stereoisomer XII was having *trans-syn-cis* configuration with equatorially oriented C-13 methyl group. Hence the overall structure of XII could be assigned as 8-aza-3-thia-A-nor-9 $\beta$ , 14 $\beta$ -estra-1, 5(10)-dien-12-one with *trans-syn-cis*-configuration.

#### Experimental Procedure

For bulb-tube distillation, air-bath temperature is given as the boiling point. Recorded temperatures are uncorrected. IR spectra were taken on a Perkin-Elmer infracord spectrophotometer model 1378, as films or solution in chloroform for liquid samples and as potassium bromide pellets for solid samples. UV spectra were determined in methanol on a Carl Zeiss RPQ-20A spectrophotometer ( $\nu_{\text{max}}$  in  $\text{cm}^{-1}$ ), PMR spectra in either  $\text{CDCl}_3$  or  $\text{CCl}_4$  on a Varian A-60A spectrometer using TMS as internal standard (chemical shifts in  $\delta$ -scale), and mass spectra on a Bausch and Lomb refractometer model ABBE-31. Silica gel (<0.08 nm) was used for column chromatography.

Table 1—IR and PMR Spectral Data of the Configurational Isomers of A-Benzenoid-3-aza-12-ketosteroid and A-Thiophen-8-aza-12-ketosteroid

Compound	Configuration*	Bohlmann-Wenkert Bands $\text{cm}^{-1}$	Chemical shift( $\delta$ ) for the C-9 proton	Chemical shift for C-18 proton in		$\delta\text{CDCl}_3-\delta\text{C}_6\text{H}_6$
				$\text{CDCl}_3$	$\text{C}_6\text{H}_6$	
XIII	<i>cis-syn-trans</i>	—	4.60	1.20	1.10	0.10
XI	<i>cis-syn-trans</i>	—	4.70	1.22	1.05	0.17
XIV	<i>trans-syn-cis</i>	2849, 2801	3.80	1.22	1.04	0.18
XII	<i>trans-syn-cis</i>	2874, 2833	3.88	1.20	1.05	0.15

\**syn* and *anti* refer to the relative configuration of the angular hydrogen at C-9 and the angular methyl group at C-13.

Anhydrous sodium sulphate was employed as drying agent.

#### Ethyl N-2-(2-thienylethyl)malonamate (III)

A mixture of 2-(2-thienyl)ethylamine (I) (8.25 g, 0.065 mol) and diethyl malonate (II) (36 g, 0.22 mol) was heated at 125–30° under nitrogen atmosphere for 8 hr. The liberated ethanol was collected in the dry ice-acetone trap. The reaction mixture was cooled and the excess of diethyl malonate distilled off at 92–94°/16 mmHg. The residue was distilled under reduced pressure at 175–80° (air-bath)/0.025 mmHg, to yield 11.7 g (74.7%) of III as a colourless liquid. The analytical sample was prepared by redistillation at 175–80° (air-bath)/0.025 mmHg,  $\eta_D^{26}$  1.5200; IR: 3333 (amide NH), 3125, 2959, 1739 (ester C=O), 1661 (amide C=O), 1550, 1439, 1370, 1333, 1031; UV: 232 nm ( $\log \epsilon$  3.95) (substituted thiophenic system); PMR ( $\text{CCl}_4$ ): 1.22 (3H, *t*,  $J=7\text{ Hz}$ ,  $\text{O}=\text{C}-\text{O}-\text{CH}_2-\text{CH}_3$ ), 4.12 (2H, *q*,  $J=7\text{ Hz}$ ,  $\text{O}=\text{C}-\text{O}-\text{CH}_2-\text{CH}_3$ ), 6.97 (3H, *m*, thiophene protons), 7.73 (1H, *m*,  $\text{O}=\text{C}-\text{H}-\text{H}$ ); MS:  $m/z$  241 ( $\text{M}^+$ ) (Found: C, 54.8; H, 6.1; N, 6.2; S, 13.5.  $\text{C}_{11}\text{H}_{15}\text{NO}_3\text{S}$  requires C, 54.8; H, 6.3; N, 5.8; S, 13.3%).

#### 1-Carbethoxymethylene-1H, 4H-2, 3-dihydrothieno[3,2-c]pyridine (IV)

To a solution of III (4.82 g, 20 mol) in dry toluene (dried over sodium, 125 ml) was added phosphorous pentoxide (18 g) in three lots at an interval of 20 min at reflux temperature. After the addition of phosphorous pentoxide was complete, the solution was further refluxed for 1.5 hr. The reaction mixture was cooled and decomposed cautiously by adding ice-cold water. The resultant mixture was filtered through celite layer. Toluene layer was separated from the filtrate and extracted with hydrochloric acid (10%, 2×10 ml). The aqueous and the acid extracts were mixed and washed with ether-benzene (2×20 ml, 1:1) to remove the unreacted amide (III). The acid portion was basified with potassium carbonate, extracted with chloroform (3×20 ml), dried and solvent removed on a water-bath.

The crude product, thus obtained, was distilled at 130–40° (air-bath)/0.1 mmHg to afford 3.5 g (78.5%) of a light yellow liquid. The analytical sample was prepared by redistillation at 130–40° (air-bath)/0.1 mmHg  $\eta_D^{24}$  1.6215; IR: 3333 (NH), 3125, 2985, 1645 (ester C=O), 1605 (enamine C=C), 1408, 1282, 1190, 1156, 1093, 1049, 881, 787; UV: 324 ( $\log \epsilon$  4.25) and 218 nm ( $\log \epsilon$  4.19) (conjugated thiophenic system); PMR ( $\text{CCl}_4$ ): 1.23 (3H, *t*,  $J=6\text{ Hz}$ ,  $\text{O}=\text{C}-\text{CH}_2-\text{CH}_3$ ), 4.05 (2H, *q*,  $J=7\text{ Hz}$ ,  $\text{O}=\text{C}-\text{OCH}_2\text{CH}_3$ ), 7.13 (2H, *m*, thiophene protons), 4.94 (1H, *s*, vinyl proton), 8.63 (1H, *m*, NH); MS:  $m/z$  223 ( $\text{M}^+$ ) (Found: C, 59.1; H, 5.8; N, 6.1; S, 13.9.  $\text{C}_{11}\text{H}_{13}\text{NO}_2\text{S}$  requires C, 59.3; H, 5.8; N, 6.1; S, 13.9%) (Found: C, 59.1; H, 5.8; N, 6.1; S, 13.9.  $\text{C}_{11}\text{H}_{13}\text{NO}_2\text{S}$  requires C, 59.3; H, 5.8; N, 6.1; S, 13.9%)

#### 1-Carbethoxymethyl-1,2,3,4-tetrahydrothieno[3,2-c]pyridine (V)

A solution of IV (6.69 g, 30 mmol) in acetic acid (30 ml) was hydrogenated over platinum oxide as catalyst (150 mg) at 50 psi in a Parr apparatus for 9 hr. More catalyst (100 mg) was then added and hydrogenation continued further for 9 hr. The catalyst was filtered and acetic acid removed under reduced pressure. The residue, thus obtained, was dissolved in water and basified with potassium carbonate. The basified solution was extracted with chloroform (3×30 ml) and dried. The solvent was removed on a water-bath and the residue distilled at 150–60° (air-bath)/0.1 mmHg to give 5.15 g (76.3%) of V as a colourless viscous product. The analytical sample was prepared by redistillation at 150–60° (air bath)/0.1 mmHg;  $\eta_D^{25}$  1.5370; IR: 3356 (NH), 2941, 1724, (ester C=O), 1445, 1370, 1282, 1170, 1031; UV: 234 ( $\log \epsilon$  3.84) (substituted thiophenic system); PMR ( $\text{CCl}_4$ ): 1.23 (3H, *t*,  $J=7\text{ Hz}$ ,  $\text{O}=\text{C}-\text{OCH}_2-\text{CH}_3$ ), 2.28 (1H, *s*,  $\text{D}_2\text{O}$  exchangeable, NH), 4.13 (2H, *q*,  $J=7\text{ Hz}$ ,  $\text{O}=\text{C}-\text{OCH}_2-\text{CH}_3$ ), 6.73 (1H, *d*,  $J=5\text{ Hz}$ , thiophene proton) and 7.02 (1H, *d*,  $J=5\text{ Hz}$ , thiophene proton); MS:  $m/z$  225 ( $\text{M}^+$ ) (Found: C, 58.5; H, 6.6; N, 6.6; S, 14.2.  $\text{C}_{11}\text{H}_{15}\text{NO}_2\text{S}$  requires C, 59.2; H, 6.7; N,

6.2; S, 14.2%)

*Condensation of 1-carbethoxymethyl-1, 2, 3, 4-tetrahydrothieno [3,2-c]pyridine (V) and cyclopentanone (VI); Formation of 8-aza-3-thia-A-norestra-1, 5(10), 13-trien -12-one (VII)*

A solution of V (3.28 g, 15 mmol) in cyclopentanone (2.52 g, 30 mmol), trifluoroacetic acid (3 ml, freshly distilled) and dry toluene (100 ml) was refluxed for 48 hr under nitrogen atmosphere. The liberated water was removed by using Dean-Stark water separator. The reaction mixture was cooled and toluene removed under reduced pressure. The residue, thus obtained, was taken up in chloroform and washed with a saturated solution of sodium bicarbonate (2×10 ml) followed by washing with brine and dried. The solvent was removed on a water-bath to give a crude product (2.7 g) which was chromatographed over silica gel (100 g, eluant: 25% acetone in chloroform). The fractions showing a single spot on TLC (silica gel, 50% acetone in chloroform) were mixed together and solvent was evaporated. The pure compound, thus obtained, was crystallised from methanol, m.p. 185–87°(d), yield 2.5 g (67.9%). An analytical sample was prepared by recrystallisation from methanol, m.p. 185–87°(d); IR: 3125, 2941, 1626, 1575, 1550, 1307, 1253, 1202, 1070, 866; UV: 232 nm (log  $\epsilon$  4.1), 329 nm (log  $\epsilon$  4.15); PMR (CDCl<sub>3</sub>): 4.65 (1H, *m*, C-9 proton), 6.84 (1H, *d*, *J*=6 Hz) and 7.23 (1H, *d*, *J*=5 Hz); MS: *m/z* 260 (M<sup>+</sup>) (Found: C, 68.3, H, 6.0; N, 6.1; S, 12.9. C<sub>14</sub>H<sub>15</sub>ONS requires C, 68.5; H, 6.1; S, 12.9%).

*11a-Methyl-1, 2, 5, 6, 9b, 10-hexahydro-11-oxo-3H, 11H-thieno[3,2-a]cyclopentano[f]quinolinium iodide (VIII)*

The enamine ketone VII (0.98 g, 4 mmol) and methyl iodide (25 ml) were refluxed in a sealed tube for 15 days at 70° in an oil-bath. The sealed tube was cooled, the solid filtered and washed thoroughly with chloroform and dried to give 1.36 g (87.9%) of a white crystalline salt. The UV spectrum of this salt exhibited maxima at 330 and 220 nm. Recrystallisation of this product from acetonitrile gave a colourless crystalline solid, m.p. 258–60°(d), yield 1.2 g (77.5%). Its UV spectrum showed an absorption maximum at 330 nm indicating the solid compound to be a C-methylated salt and that the crude product was a mixture of C-methylated and O-methylated salts.

An analytical sample was prepared by recrystallisation from acetonitrile, m.p. 258–60°(d); IR: 3077, 2941, 1730, 1667, 1449, 1309, 1282, 1136, 1106, 990, 838, 760; UV: 220 nm (log  $\epsilon$  3.99), PMR (CDCl<sub>3</sub>): 1.77 (3H, *s*, C-13CH<sub>3</sub>), 6.0 (1H, *m*, C-9 proton), 6.96 (1H, *d*, *J*=5 Hz) and 7.43 (1H, *d*, *J*=6 Hz); (Found: C, 46.5; H,

4.75; N, 3.8; S, 8.6; I, 32.0. C<sub>15</sub>H<sub>18</sub>INOS requires C, 46.5; H, 4.60; N, 3.6; S, 8.3; I, 32.8%).

*Lithium aluminium hydride reduction of VIII and Jone's oxidation of the resultant mixture of alcohols (X): Formation of XI and XII*

A suspension of the finely powdered salt VIII (0.6 g, 1.55 mmol) in dry tetrahydrofuran (20 ml, dried over lithium aluminium hydride) was added to the stirred suspension of lithium aluminium hydride (0.57 g, 15 mmol) in tetrahydrofuran (20 ml) under nitrogen atmosphere at room temperature. After the addition was over, the mixture was refluxed for 4 hr, cooled and decomposed cautiously by adding ethyl acetate (1 ml) followed by the addition of sodium hydroxide solution (10%, 2 ml). The resultant mixture was filtered and the solvent removed on a water-bath, the last traces being removed under reduced pressure. The residue, thus obtained, was dissolved in benzene, the solution dried and solvent removed on a water-bath, the last traces of solvent were removed under reduced pressure. This afforded 0.33 g (80.9%) of the crude mixture of isomeric alcohols (X). The IR spectrum showed a band at 3448 for the hydroxyl group whereas the band for the carbonyl group around 1730 was absent. This crude mixture of the isomeric alcohols was oxidised using Jone's reagent without further purification, as follows:

To the ice cooled solution of X (0.33 g, 1.26 mmol) in acetone (10 ml) was added dropwise Jone's reagent (2.5 ml) under stirring. After the addition was complete, the reaction mixture was stirred further for 2.5 hr at 0°, water (20 ml) added and acetone removed under reduced pressure. More water was added to the residue and the resultant aq. solution basified with potassium hydroxide pellets. The basic solution was extracted with chloroform (3×20 ml) and dried. The solvent was removed on a water-bath, the last traces being removed under reduced pressure, to give 0.2 g of the mixture of crude aminoketones. The separation of the mixture was achieved by column chromatography over silica gel (40 g, eluant: 10% ethyl acetate in benzene). The product having higher *R<sub>f</sub>* was separated and purified by crystallisation from pet. ether (60–80°), m.p. 74–76°, yield 112 mg (34.2%). The other product having lower *R<sub>f</sub>* was also similarly separated and crystallised from pet. ether (60–80°), m.p. 100–102°, yield 85 mg (26%).

An analytical sample of the product having lower *R<sub>f</sub>* (XI) was prepared by recrystallisation from pet. ether (60–80°), m.p. 102–3°, IR: 2985, 1718, 1429, 1285, 1179, 1149, 1087, 1055; UV: 236 nm (log  $\epsilon$  3.77); PMR (CDCl<sub>3</sub>): 1.22 (3H, *s*, C-13 CH<sub>3</sub>), 4.7 (1H, *m*, C-8 proton), 6.91 (1H, *d*, *J*=5 Hz) and 7.14 (1H, *d*, *J*=5 Hz); MS: *m/z* 261 (M<sup>+</sup>) (Found: C, 68.8; H, 7.4; N, 5.2; S,

12.0. C<sub>15</sub>H<sub>19</sub>NOS requires C, 68.9; H, 7.3, N, 5.3; S, 12.2%)

An analytical sample of the compound having higher *R<sub>f</sub>* (XII) was prepared by recrystallisation from pet. ether (60-80°), m.p. 75-76°, IR: 2985, 2874, 2833, 1701, 1460, 1351, 1311, 1282, 1093, 844; UV: 232 nm (log  $\epsilon$  3.83); PMR (CDCl<sub>3</sub>): 1.2 (3H, *s*, C-13 CH<sub>3</sub>), 6.76(1H, *d*, *J*=5 Hz) and 7.17(1H, *d*, *J*=6 Hz); 3.88(1H, *m*, C-9 proton); MS: *m/z* 261 (M<sup>+</sup>) (Found: C, 68.8; H, 7.3; N, 5.4; S, 12.6. C<sub>15</sub>H<sub>19</sub>NOS requires C, 68.9; H, 7.3, N, 5.4; S, 12.3%)

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## The Schmidt Reaction : Synthesis of Azasteroids

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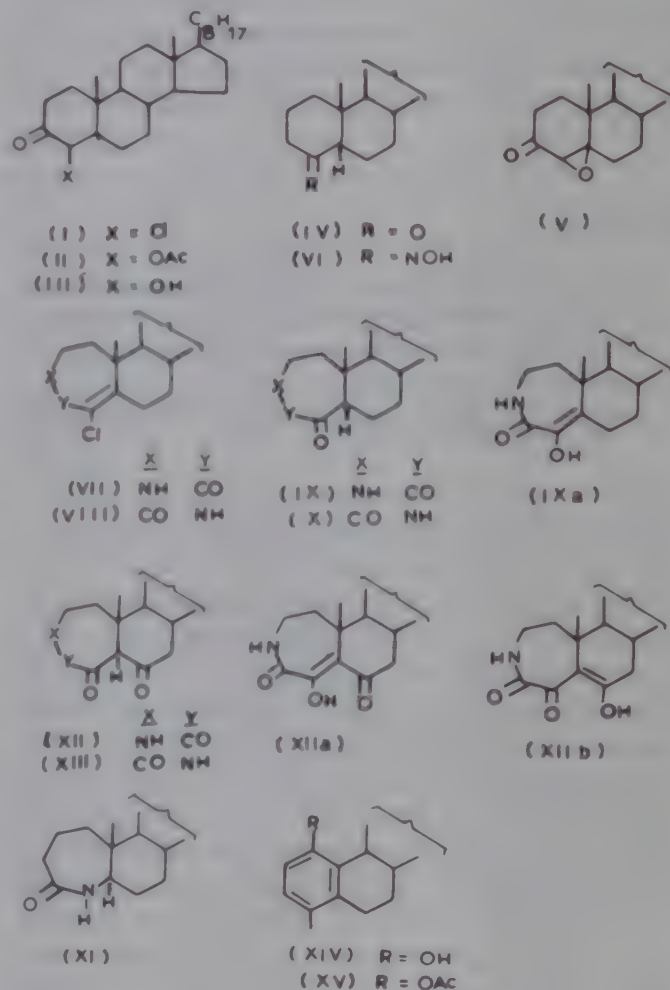
The Schmidt reaction on 4-chlorocholest-4-en-3-one (I), its 4-acetoxy (II) and 4-hydroxy (III) analogues, 5 $\alpha$ -cholestan-4-one (IV) and 4 $\beta$ ,5-epoxy-5 $\beta$ -cholestan-3-one (V) gives the lactams (VII), (IX), (XI) and (XII), respectively. The ketone (V) also affords the ring-A aromatized product (XIV). These compounds have been characterized on the basis of their elemental analyses and spectral data. Formation of XII and XIV from V has been rationalised.

In continuation of our previous work on azasteroids<sup>1</sup> we now report the Schmidt reaction on the ketones (I-V).

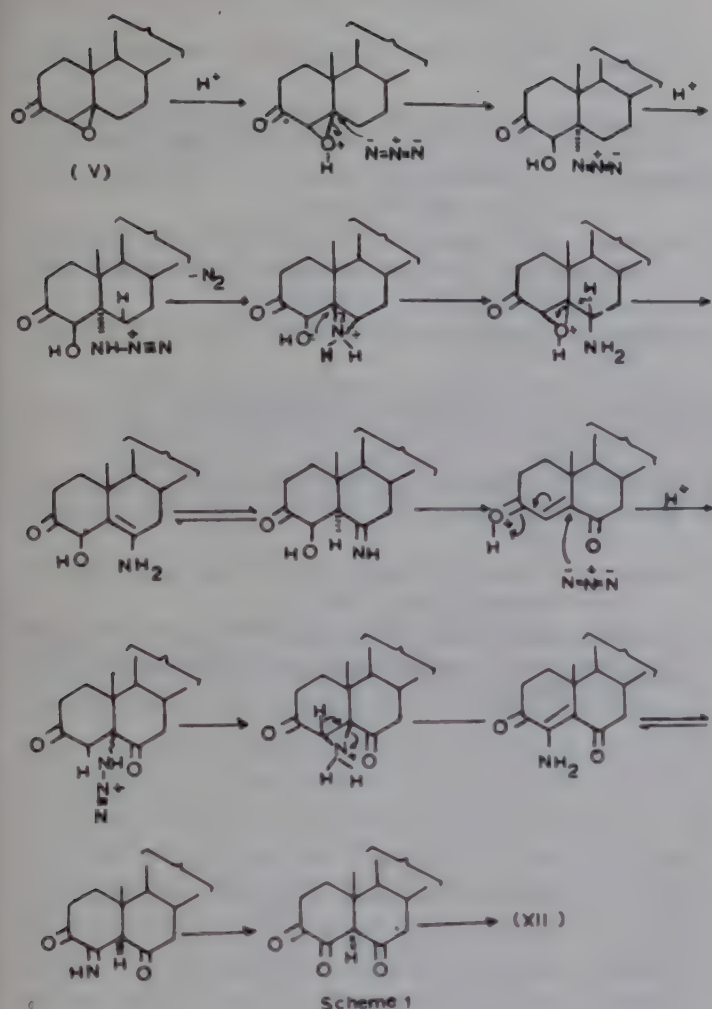
4-Chlorocholest-4-en-3-one (I) on treatment with sodium azide (1 mol equiv.) in PPA afforded 3-aza-4a-chloro-A-homocholest-4a-en-4-one (VII) and not its isomer (VIII). The characterization of the lactam (VII) is based on its elemental analyses, and spectral data (see Experimental).

Similar treatment of 4-acetoxycholest-4-en-3-one (II) afforded a product which on spectral data was formulated as 3-aza-A-homo-5 $\alpha$ -cholestan-4,4a-dione (IX). The isomeric structure (X) was ruled out on spectral considerations. In this case, besides nitrogen insertion, hydrolysis of the acetate function also occurred. IX is expected to be in equilibrium with IXa<sup>2</sup>. 4-Hydroxycholest-4-en-3-one (III) under similar conditions also afforded the lactam (IX). The Schmidt reaction on 5 $\alpha$ -cholestan-4-one (IV) led to 4a-aza-A-homo-5 $\alpha$ -cholestan-4-one (XI). The lactam (XI) was also obtained from the Beckmann rearrangement of the oxime (VI)<sup>3</sup>.

4 $\beta$ ,5-Epoxy-5 $\beta$ -cholestan-3-one (V) on Schmidt reaction gave two products, 3-aza-A-homo-5 $\alpha$ -cholestan-4,4a,6-trione (XII) and 1-hydroxy-4-methyl-19-norcholesta-1,3,5(10)-triene (XIV). Both the products are not the most expected ones from such a reaction and their identity and formation have been discussed in some length. XII analysed for C<sub>27</sub>H<sub>43</sub>NO<sub>3</sub> and its IR spectrum displayed bands at 3220, 3140 (CONH), 1725, 1695 and 1668 cm<sup>-1</sup>, which clearly indicated the presence of three carbonyl groups as in the proposed structure (XII). The PMR spectrum of XII exhibited a three-proton multiplet at  $\delta$  3.3 which could be attributed to -N-C<sub>2</sub>-H<sub>2</sub> and C<sub>5</sub>- $\alpha$ H thus ruling out the possibility of the alternate structure (XIII)<sup>4,5</sup>. Of course XII is expected to be in equilibrium with XIIa and XIIb<sup>5,6</sup>. The formation of XII from V under the Schmidt conditions has been rationalized in Scheme 1<sup>cf 4</sup>.



Compound (XIV) analysed for C<sub>27</sub>H<sub>42</sub>O and its IR spectrum displayed peaks at 3495, 3390 (OH) and 1585 cm<sup>-1</sup> (aromatic). The presence of the aromatic ring was further supported by its UV spectrum ( $\lambda_{\max}$  248, 282 nm). Its PMR spectrum exhibited two doublets of one proton each at  $\delta$  6.86 and 6.4 ( $J$  = 8.5 Hz). This is clearly a case of *ortho*-coupling as shown in XIV<sup>7</sup>. The hydroxyl proton appeared at  $\delta$  4.53 (disappeared on the addition of D<sub>2</sub>O). The C<sub>4</sub>-methyl appeared as a singlet at  $\delta$  2.16.



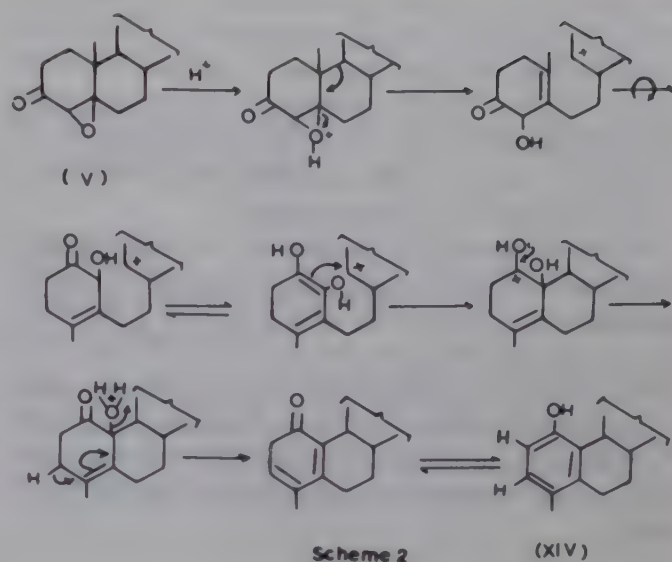
XIV on treatment with acetic anhydride gave the acetate (XV). The formation of XIV from V is rationalised in Scheme 2<sup>8</sup>.

### Experimental Procedure

Melting points were taken in open capillaries and are uncorrected. IR spectra were recorded in KBr ( $\nu_{\max}$  in  $\text{cm}^{-1}$ ) on a Pye-Unicam SP3-100 spectrophotometer, UV spectra in methanol ( $\lambda_{\max}$  in nm) on a Beckman DK-2 spectrophotometer and PMR spectra in  $\text{CDCl}_3$  on a Varian A60 D instrument, with TMS as an internal standard: chemical shifts in  $\delta$  scale. Light petroleum refers to fraction, b.p. 60–80°.

#### Schmidt reaction on ketones (I–V)

The ketone (I)<sup>9</sup> (1.5 g) in PPA [freshly prepared from  $\text{P}_2\text{O}_5$  (22 g) and  $\text{H}_3\text{PO}_4$  (15 ml)] was heated to 50–60° and sodium azide (200 mg) added to it slowly with stirring. The reaction mixture was kept at this temperature for 6 hr, poured onto crushed ice-water mixture, extracted with chloroform and the organic extract successively washed with water, aq sodium bicarbonate and water and dried ( $\text{Na}_2\text{SO}_4$ ). Removal of solvent gave an oil which crystallized from light petroleum to give VII (800 mg), m.p. 156°; positive Beilstein test (Found: C, 74.5; H, 10.0;



N, 3.1.  $\text{C}_{27}\text{H}_{44}\text{NOCl}$  requires C, 74.7; H, 10.2; N, 3.3%; IR: 3215, 3080 (NH), 1665 (CONH), 1640sh, 1565w [ $\text{C}=\text{C}(\text{Cl})-\text{C}=\text{O}$ ], 710 ( $\text{C}-\text{Cl}$ )<sup>4</sup>; UV: 235; PMR: 8.6 (*m*, 1H, CONH, exchangeable with  $\text{D}_2\text{O}$ ), 3.2 (*m*, 2H,  $\text{C}_2-\text{H}_2$ )<sup>4</sup>, 1.21, 0.91, 0.83 and 0.7 (methyl protons).

Under similar reaction conditions II<sup>10</sup> and III<sup>11</sup> afforded one and the same lactam (IX) which crystallized from light petroleum (1 g of II and III gave 550 mg and 600 mg of IX respectively), m.p. 194° (Found: C, 77.8; H, 10.7; N, 3.1.  $\text{C}_{27}\text{H}_{45}\text{NO}_2$  requires C, 78.0; H, 10.9; N, 3.4%; IR: 3220, 3100 (NH), 1700 ( $\text{C}_4=\text{C}$ -carbonyl), 1680 (CONH); PMR: 7.58 (*m*, 1H, CONH, disappears on addition of  $\text{D}_2\text{O}$ ), 3.38 (*m*, 2H,  $\text{C}_2-\text{H}_2$ )<sup>4</sup>, 2.58 (*t*, 1H,  $\text{C}_5-\alpha\text{H}$ ), 1.06, 0.98, 0.81 and 0.68 (methyl protons).

IV<sup>12</sup> (200 mg) under similar reaction conditions gave the lactam (XI), which crystallized from acetone (50 mg), m.p. 221° (lit.<sup>3</sup> m.p. 221°) (Found: C, 80.5; H, 11.7; N, 3.3. Calc for  $\text{C}_{27}\text{H}_{47}\text{NO}$ : C, 80.7; H, 11.8; N, 3.5%; IR: 3200 (NH), 1660 (CONH); PMR: 5.3 (br, 1H, CONH, disappears on addition of  $\text{D}_2\text{O}$ ), 3.2 (*m*, 1H,  $\text{C}_5-\alpha\text{H}$ ), 2.48 (*m*, 2H,  $\text{C}_3-\text{H}_2$ ), 1.0, 0.91, 0.85 and 0.68 (methyl protons).

The epoxy ketone (V)<sup>9</sup> (3 g) under similar treatment followed by column chromatography gave two products. Elution with 10:1 light petroleum-ether afforded XIV, which crystallized from methanol (650 mg), m.p. 140° (lit.<sup>13</sup> m.p. 146°) (Found: C, 84.5; H, 10.9. Calc for  $\text{C}_{27}\text{H}_{42}\text{O}$ : C, 84.8; H, 11.1%; IR: 3494, 3390 (OH), 1585 ( $\text{C}=\text{C}$ , aromatic); UV: 248, 282; PMR: 6.86 (*d*, 1H,  $\text{C}_3-\text{H}$ ,  $J=8.5\text{ Hz}$ ), 6.4 (*d*, 1H,  $\text{C}_2-\text{H}$ ,  $J=8.5\text{ Hz}$ ), 4.53 (*br*, 1H,  $\text{C}_1-\text{OH}$ ), 2.16 (*s*, 3H,  $\text{C}_4-\text{CH}_3$ ), 0.95, 0.86 and 0.76 (other methyls).

Acetylation of XIV (pyridine- $\text{Ac}_2\text{O}$ ) after usual work-up followed by chromatography gave the

acetate (XV) as a non-crystallizable oil (Found: C, 81.9; H, 10.3.  $C_{29}H_{44}O_2$  requires C, 82.0; H, 10.4%); IR: 1760 (enol acetate)<sup>14</sup>, with shoulder at 1700, 1585w (C=C, aromatic), 1225 (acetate); PMR: 6.8 (d, 1H,  $C_3$ -H,  $J=8.5$ Hz), 6.6 (d, 1H,  $C_2$ -H,  $J=8.5$ Hz), 2.16 (bs, 6H,  $C_4$ -CH<sub>3</sub> and OCOCH<sub>3</sub>), 0.91, 0.83 and 0.71 (other methyls).

Further elution of the column with 4:1 light petroleum-ether afforded XII, which crystallized from methanol (1.2 g), m.p. 191° (Found: C, 75.3; H, 10.0; N, 3.2.  $C_{27}H_{43}NO_3$  requires C, 75.5; H, 10.1; N, 3.3%); IR: 3220, 3140 (NH), 1725, 1695 ( $C_6$  and  $C_{4a}$ -carbonyls), 1668 (CONH); PMR: 8.1 (br, 1H, CONH, exchangeable with D<sub>2</sub>O), 3.3 (m, 3H,  $C_2$ -H<sub>2</sub> and  $C_5$ -αH)<sup>4,5</sup>, 1.0, 0.91, 0.83 and 0.68 (methyl protons).

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# $\alpha$ , $\beta$ -Unsaturated N-Acylureas as Useful Intermediates for the Synthesis of Indanones, Chromanones & Coumarins

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$\alpha$ ,  $\beta$ -Unsaturated N-acylureas, viz-N-formamido-2-butenamide (I), N-formamido-3-methyl-2-butenamide (II) and N-formamido-3-phenyl-2-propanamide (III) react with aryl alkyl ethers in the presence of PPA to afford the corresponding crotonophenones and chalcones (IV) at lower temperature and l-indanones (V) at a higher temperature. Reactions of I and II with phenols in the presence of PPA afford the 4-chromanones (VI), while III gives 3,4-dihydro-4-phenylcoumarins (VII) in excellent yields.

Recently, in our laboratory<sup>1,2</sup>, N-acylureas have been found to be better acylating agents than the corresponding free acids. In an effort to realise the utility of such an approach for the synthesis of naturally occurring indanones, chromanones and coumarins, the reactions of  $\alpha$ ,  $\beta$ -unsaturated N-acylureas, viz. N-formamido-2-butenamide (I)<sup>3</sup>, N-formamido-3-methyl-2-butenamide (II)<sup>4</sup> and N-formamido-3-phenyl-2-propanamide (III)<sup>5</sup> with phenols and aryl alkyl ethers were investigated. The present paper describes the use of I, II and III as reagents for the synthesis of crotonophenones, chalcones, l-indanones, 4-chroma-

nones and 3,4-dihydro-4-phenylcoumarins under acid catalysed reaction conditions (Chart 1).

Experimental results (Tables 1 and 2) have revealed that the ureas (I-III) could be effectively employed in the presence of PPA for nuclear acylation of aryl alkyl ethers to give selectively the respective crotonophenone and chalcone derivatives (IV) at lower temperature and the respective l-indanone derivatives (V) at a

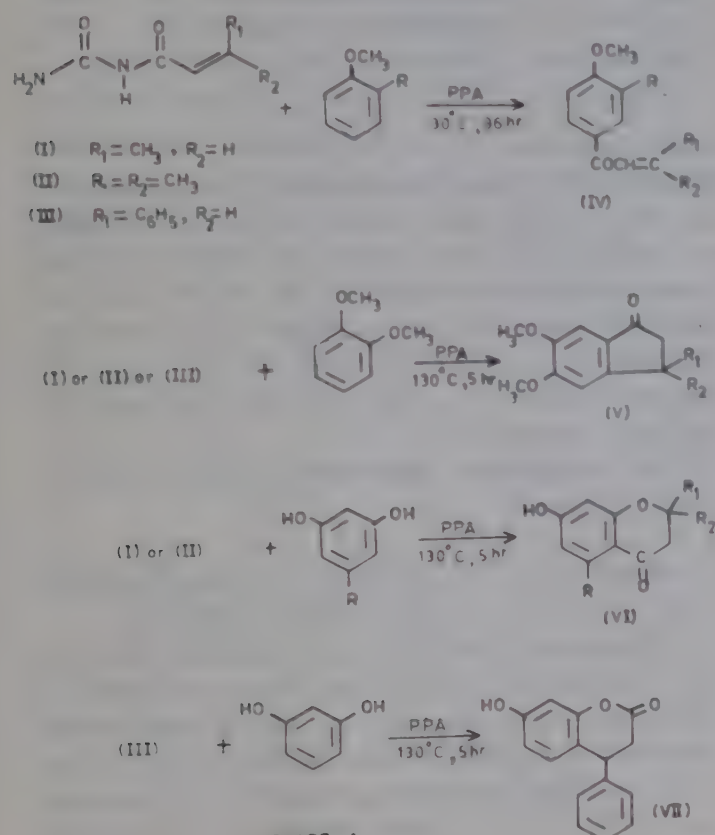


CHART 1

Table 1 Reactions of  $\alpha$ ,  $\beta$ -Unsaturated N-Acylureas (I-III) with Aryl Alkyl Ethers in PPA at  $30^\circ\text{C}$  for 96 hr

Aryl alkyl ether	Product (m.p. or b.p.) $^\circ\text{C}$	Yield %
Reaction with I		
Anisole	4'-Methoxycrotonophenone (b.p. 116-0.01 mm) <sup>11</sup>	75
Veratrole	3',4'-Dimethoxycrotonophenone (m.p. 55) <sup>9</sup>	65
Resorcinol dimethyl ether	2',4'-Dimethoxycrotonophenone (b.p. 125/0.3 mm) <sup>12</sup>	80
Hydroquinone dimethyl ether	2',5'-Dimethoxycrotonophenone (b.p. 158-60/1 mm) <sup>13</sup>	65
Reaction with II		
Anisole	4'-Methoxy-3-methylcrotonophenone (b.p. 80-90/0.2 mm) <sup>14</sup>	60
Resorcinol dimethyl ether	2',4'-Dimethoxy-3-methylcrotonophenone (b.p. 152-53/3 mm) <sup>15</sup>	65
Hydroquinone dimethyl ether	2',5'-Dimethoxy-3-methylcrotonophenone (b.p. 165-68/5 mm) <sup>16</sup>	60
Reaction with III		
Anisole	4'-Methoxychalcone (m.p. 107) <sup>17</sup>	70
Veratrole	3',4'-Dimethoxychalcone (m.p. 83) <sup>18</sup>	80
Resorcinol dimethyl ether	2',4'-Dimethoxychalcone (m.p. 81) <sup>19</sup>	75
Hydroquinone dimethyl ether	2',5'-Dimethoxychalcone (m.p. 160) <sup>20</sup>	65

Table 2—Reactions of  $\alpha$ ,  $\beta$ -Unsaturated N-Acylureas (I-III) with Aryl Alkyl Ethers in PPA at 130°C for 5 hr

Aryl alkyl ether	Product (m.p. or b.p.)°C	Yield %
Reaction with I		
Anisole	5-Methoxy-3-methyl-1-indanone (m.p. 51) <sup>21</sup>	70
Veratrole	5,6-Dimethoxy-3-methyl-1-indanone (m.p. 90-92) <sup>6</sup>	70
Reaction with II		
Anisole	3,3-Dimethyl-5-methoxy-1-indanone (b.p. 175-76/16 mm) <sup>22</sup>	70
Veratrole	3,3-dimethyl-5,6-dimethoxy-1-indanone (m.p. 71) <sup>6</sup>	75
Hydroquinone dimethyl ether	4,7-Dimethoxy-3,3-dimethyl-1-indanone (m.p. 90) <sup>23</sup>	60
Reaction with III		
Veratrole	5,6-Dimethoxy-3-phenyl-1-indanone (m.p. 108) <sup>6</sup>	80

higher temperature in good yields. These results are significant as earlier work<sup>6</sup> on the reactions of  $\alpha$ ,  $\beta$ -unsaturated acids with aryl alkyl ethers in the presence of PPA resulted in a mixture of  $\alpha$ ,  $\beta$ -unsaturated carbonyl compounds and 1-indanones even under controlled conditions. Further, when I and II were reacted with phenols in the presence of PPA, 4-chromanones were obtained in a single step in excellent yields (Table 3); even the 2-methyl-4-chromanones (VI), which are reported in literature to have been obtained in low yields by the conventional methods<sup>7-10</sup>, could be obtained in excellent yields. This could be attributed to the fact that use of free acid or acid chloride leads to the formation of the intermediate O-acyl derivatives or crotonophenones which need to be further converted into the desired product in a separate step. The reaction of III with phenols in the presence of PPA (Table 4) afforded in one-step 3,4-dihydro-4-phenylcoumarin derivatives (VII) in excellent yields. Formation of coumarin derivatives (VII) and not chromanone derivatives (VII) may be attributed to the difference in reactivity of the double bond in I, II and III.

The simple acylureas, such as I-III thus participate in the trans-acylation reactions leading to a one-step synthesis of crotonophenones, chalcones, 1-indanones and 4-chromanones involving the transfer of C-4, C-5 and C-9 units respectively from nitrogen of urea derivative to the nuclear C-atom.

#### Experimental Procedure

3',4'-Dimethoxycrotonophenone (IV:  $R = OCH_3$ ,  $R_1 = CH_3$  and  $R_2 = H$ ).

A mixture of veratrole (2.76 g, 0.02 mol), I (2.56 g, 0.02 mol) and PPA (32 g) was allowed to stand at room

Table 3—Reactions of  $\alpha$ ,  $\beta$ -Unsaturated N-Acylureas (I and II) with Phenols in PPA at 130°C for 5 hr

Phenol	Product (m.p.°C)	Yield %
Reaction with I		
Phenol	2-Methyl-4-chromanone (32) <sup>7</sup>	60
Resorcinol	7-Hydroxy-2-methyl-4-chromanone (165-66) <sup>8</sup>	80
Phloroglucinol	5,7-Dihydroxy-2-methyl-4-chromanone (175-76) <sup>9</sup>	82
Orcinol	7-Hydroxy-2, 5-dimethyl-4-chromanone (170) <sup>10</sup>	85
Reaction with II		
Phenol	2,2-Dimethyl-4-chromanone (88-89) <sup>24</sup>	60
Resorcinol	7-Hydroxy-2, 2-dimethyl-4-chromanone (172) <sup>25</sup>	80
Phloroglucinol	5,7-Dihydroxy-2, 2-dimethyl-4-chromanone (198) <sup>26</sup>	90
Orcinol	7-Hydroxy-2, 2,5-trimethyl-4-chromanone (190) <sup>27</sup>	85
Methyl 3,5-dihydroxybenzoate	5-Carbomethoxy-7-hydroxy-2,2-dimethyl-4-chromanone (194)	60

Table 4 Reaction of III with Phenols in PPA at 130°C for 5 hr

Phenol	Product (m.p.°C)	Yield %
Phenol	3,4-Dihydro-4-phenylcoumarin (83) <sup>28</sup>	70
Resorcinol	3,4-Dihydro-7-hydroxy-4-phenylcoumarin (140) <sup>28</sup>	75
Phloroglucinol	3,4-Dihydro-5,7-dihydroxy-4-phenylcoumarin (204-5) <sup>29</sup>	75
Orcinol	3,4-Dihydro-7-hydroxy-5-methyl-4-phenylcoumarin (163) <sup>28</sup>	80

temperature for 96 hr. the reaction mixture was poured over crushed ice, extracted with ether (2 × 15 ml), the combined ether extract washed with saturated aq NaHCO<sub>3</sub> (25 ml), water and dried (Na<sub>2</sub>SO<sub>4</sub>). Removal of the solvent gave a solid, which crystallised from pet. ether-benzene to afford IV in colourless needles (2.7 g, yield 65%), m.p. 55° (lit.<sup>6</sup> m.p. 55°), identical (co-TLC, co-IR and m.m.p.) with the authentic<sup>6</sup> sample of IV.

Other compounds mentioned in Table 1 were similarly prepared.

5-Carbomethoxy-7-hydroxy-2, 2-dimethyl-4-chromanone (VI:  $R_1 = R_2 = CH_3$  and  $R = COOCH_3$ )

A mixture of veratrole (2.76 g, 0.02 mol), III (3.8 g, 0.02 mol) and PPA (32 g) was heated in oil-bath at 130°C for 5 hr. The reaction mixture was cooled, poured onto crushed ice and the resulting colourless solid was filtered, washed successively with saturated aq NaHCO<sub>3</sub> (30 ml), water and dried. Crystallisation

from chloroform gave V as colourless prisms (4.2 g, yield 80%), m.p. 180° (lit.<sup>6</sup> m.p. 108°), identical (co-TLC, co-IR, m.m.p.) with the authentic<sup>6</sup> sample of V.

Similarly, other compounds listed in Table 2 were synthesised.

### 5-Carbomethoxy-7-hydroxy-2, 2-dimethyl-4-chromanone (VI: $R_1 = R_2 = CH_3$ and $R = COOCH_3$ )

A mixture of methyl 3,5-dihydroxybenzoate (3.36 g, 0.02 mol), II (2.84 g, 0.02 mol) and PPA (32 g) was heated in oil-bath at 130°C for 5 hr and worked-up as described above to give a solid. It was purified by column chromatography over silica gel. Elution with benzene gave a fraction which on removal of the solvent afforded the title compound as a solid, which crystallised from methanol as colourless needles (3 g, yield 60%), m.p. 194° (Found: C, 62.6; H, 5.5  $C_{13}H_{14}O_5$  requires C, 62.4; H, 5.6%); IR (KBr): 1690 (non-bonded chromanone carbonyl), 1770 ( $-COOCH_3$ ) and 3400  $cm^{-1}$  ( $-OH$ ); PMR ( $CDCl_3$ ):  $\delta$  1.5 (s, 6H, gem-dimethyl), 2.6 (s, 2H,  $COCH_2$ ), 3.9 (s, 3H,  $-COOCH_3$ ), 7.3 (d, 2H, Ar-H) and 10.8 (s, 1H,  $-OH$ ,  $D_2O$  exchangeable).

Similarly, other compounds listed in Table 3 were synthesised.

### 3,4-Dihydro-7-hydroxy-4-phenylcoumarin (VII)

A mixture of resorcinol (2.2 g, 0.02 mol), III (3.8 g, 0.02 mol) and PPA (32 g) was heated in oil-bath at 130°C for 5 hr and worked-up as described earlier to give a solid, which crystallised from chloroform as colourless prisms (3.6 g, yield 75%), m.p. 140° (lit.<sup>28</sup> m.p. 140°), identical (co-TLC, co-IR and m.m.p.) with the authentic<sup>28</sup> sample of VII.

Similarly, other coumarins listed in Table 4 were prepared.

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# Reaction of 2-Aminobenzoylhydrazines with Hexan-2,5-dione & $\beta$ -Keto Esters: Formation of Pyridazine, Pyrrole & Pyrazolo[5,1-*b*]quinazolinone Derivatives

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The reactions of 2-aminobenzoylhydrazines (**1**) with hexan-2,5-dione, ethyl acetoacetate and ethyl benzoylacetate are reported. With hexan-2,5-dione, 1-(2'-amino/alkylaminobenzoyl)-3,6-dimethyl-1,2-dihydropyridazines (**2**) and/or 1-(2'-amino/alkylaminobenzoylamino)-2,5-dimethylpyrroles (**3**) are formed depending on the experimental conditions. With ethyl acetoacetate and ethyl benzoylacetate, the corresponding 2,4-disubstituted-9-oxo-pyrazolo[5,1-*b*]quinazolines (**10** and **11**) are obtained as the final products.

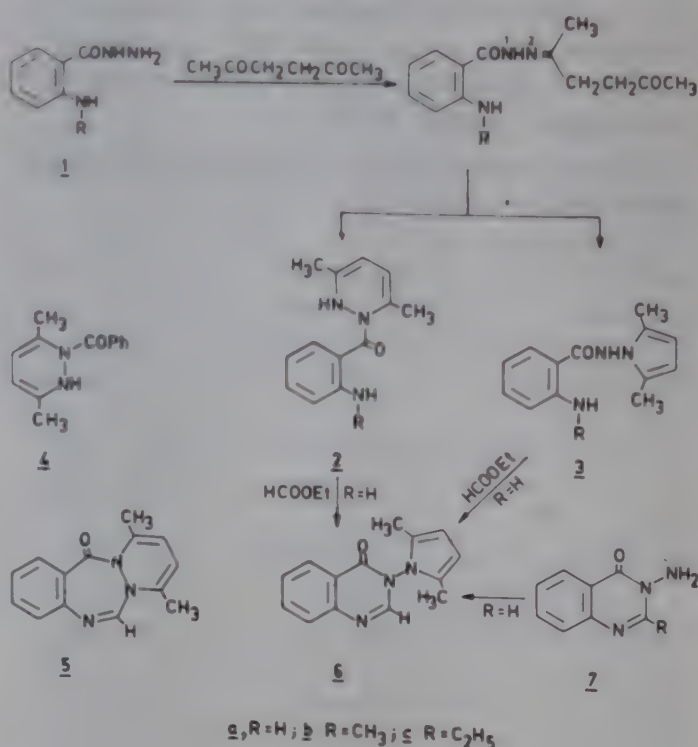
The therapeutic and commercial success of fused 1,4-benzodiazepinones as CNS depressants and antibiotics has stimulated considerable interest in the related systems. As part of a general scheme to synthesise suitable intermediates having fused 1,3,4-benzotriazepin-5-ones, which are the aza analogues of 1,4-benzodiazepinones, the reactions of 2-aminobenzoylhydrazines (**1**) with hexan-2,5-dione and  $\beta$ -keto esters have been studied, and the results presented here.

2-Aminobenzoylhydrazine (**1a**) reacts readily with hexan-2,5-dione in triethylamine to yield 1-(2'-aminobenzoyl)-3,6-dimethyl-1,2-dihydropyridazine (**2a**). In ethanol containing a small amount of *p*-toluenesulfonic acid, the reaction however, leads to 1-(2'-aminobenzoylamino)-2,5-dimethylpyrrole (**3a**) which is isomeric with **2a**. In ethanol alone, a mixture of **2a** (33%) and **3a** (47%) is obtained. 2-Methylamino-(**1b**)- and 2-ethylamino-(**1c**)-benzoylhydrazine also react similarly with hexan-2,5-dione. The structures of **2** and **3** have been ascertained from their spectral (IR, PMR and Mass) and analytical data (Table 1).

The PMR spectrum of **2a** looks similar to that of 1-benzoyl-3,6-dimethyl-1,2-dihydropyridazine<sup>1</sup> (**4**) with comparable  $\delta$ -values for methyl ( $\delta$  2.49) and olefinic ( $\delta$  6.18) protons. In **3a**, these protons appear at  $\delta$  2.09 and 5.82 respectively similar to those in 2,5-dimethylpyrrole<sup>2</sup>. Compounds **2a** and **3a** also show considerable differences in their mass spectra. Thus, **2a** displays prominent ions due to 2-aminobenzoyl cation ( $m/z$  120) and 3,6-dimethyl-1,2-dihydropyridazine ion ( $m/z$  109) while N-N bond cleavage fragments, 2,5-dimethylpyrrolonium ( $m/z$  94) and 2-aminobenzamide ( $m/z$  136), characterise the spectrum of **3a**. The formation of **2a** and

**3a** could be explained through the intermediacy of hydrazone (Scheme 1), which undergoes cyclisation involving the amide nitrogen ( $N^1$ ) or the alkylidene nitrogen ( $N^2$ ) and the reaction pathway seems to be entirely dependent on the reaction conditions used.

In order to synthesise 1,4-dimethyl-11-oxo-pyridazino[2,1-*c*]1,3,4-benzotriazepine (**5**), **2a** was refluxed with excess ethyl formate. The product formed ( $M^{+}$  at  $m/z$  239) was devoid of NH absorptions in the IR spectrum which exhibited the  $\nu C=O$  mode at  $1705\text{ cm}^{-1}$ . The PMR spectrum of the product displayed signals for two olefinic pro-



Scheme 1

Table 1—Characterisation Data of 1-(2'-Amino/alkylaminobenzoyl)-3,6-dimethyl-1,2-dihydropyridazines (**2**) and 1-(2'-Amino/alkylaminobenzoylamino)-2,5-dimethylpyrroles (**3**)

Compd	R	m.p. (°C)	Yield (%)	Mol. formula* (M <sup>+</sup> )	IR (cm <sup>-1</sup> )		PMR (δ ppm)			
					νC=O	νNH	Methyl	NH	Aromatic ( <i>m</i> , 4H)	Others
<b>2a</b>	H	153	83	C <sub>13</sub> H <sub>15</sub> N <sub>3</sub> O (229)	1645	3200 3350 3400	2.49 ( <i>s</i> , 6H, 2 × =C-CH <sub>3</sub> )	6.88 ( <i>s</i> , 2H)	7.04-8.19	6.18 ( <i>s</i> , 2H, 2 × =CH)
<b>2b</b>	CH <sub>3</sub>	178	85	C <sub>14</sub> H <sub>17</sub> N <sub>3</sub> O (243)	1645	3200 3310	2.46 ( <i>s</i> , 6H, 2 × =C-CH <sub>3</sub> )	5.87 ( <i>s</i> , 1H)	7.0-8.27	6.10 ( <i>s</i> , 2H, 2 × =CH)
<b>2c</b>	C <sub>2</sub> H <sub>5</sub>	162	80	C <sub>15</sub> H <sub>19</sub> N <sub>3</sub> O (257)	1640	3190 3300	2.91 ( <i>s</i> , 3H, N-CH <sub>3</sub> ) 1.12 ( <i>t</i> , 3H, CH <sub>3</sub> )	6.4 ( <i>s</i> , 1H)	6.92-8.36	3.05 ( <i>q</i> , 2H, N-CH <sub>2</sub> )
<b>3a</b>	H	156	65	C <sub>13</sub> H <sub>15</sub> N <sub>3</sub> O (229)	1680	3250 3400 3460	2.09 ( <i>s</i> , 6H, 2 × =C-CH <sub>3</sub> )	5.512 ( <i>s</i> , 2H)	6.65-7.4	5.829 ( <i>s</i> , 2H, 2 × =CH)
<b>3b</b>	CH <sub>3</sub>	151	61	C <sub>14</sub> H <sub>17</sub> N <sub>3</sub> O (243)	1675	3220 3350	2.1 ( <i>s</i> , 6H, 2 × =C-CH <sub>3</sub> )	5.64 ( <i>s</i> , 1H)	6.53-7.49	5.852 ( <i>s</i> , 2H, 2 × =CH)
<b>3c</b>	C <sub>2</sub> H <sub>5</sub>	145	60	C <sub>15</sub> H <sub>19</sub> N <sub>3</sub> O (257)	1675	3250 3350	2.95 ( <i>s</i> , 3H, N-CH <sub>3</sub> ) 1.2 ( <i>t</i> , 3H, CH <sub>3</sub> )	8.2 ( <i>s</i> , 1H) 6.1 ( <i>s</i> , 1H)	6.50-7.58	5.81 ( <i>s</i> , 2H, 2 × =CH)
							2.13 ( <i>s</i> , 6H, 2 × =C-CH <sub>3</sub> )	8.7 ( <i>s</i> , 1H)		3.1 ( <i>q</i> , 2H, N-CH <sub>2</sub> )

\*Satisfactory analytical data were obtained: C, ±0.042; H, ±0.02; N, ±0.032.

tons (*s*, δ 5.94), one azomethine proton (*s*, 7.25) and four aromatic protons (*m*, 7.6-8.4). Though these spectral data seem compatible with the expected benzotriazepinone structure (**5**), the appearance of an ion fragment at *m/z* 94 (2,5-dimethylpyrrolium cation) as the base peak in its mass spectrum is strongly suggestive of the isomeric 3-(2',5'-dimethylpyrrolo)quinazolin-4(3*H*)-one structure (**6**) for the product. That the product has structure (**6**) was confirmed by synthesising **6** from **3a** and from 3-aminoquinazolin-4(3*H*)-one (**7**, R=H). The formation of **6** from **2a** obviously involves benzotriazepinone-quinazolinone ring transformation, the mechanism of which is not clear.

Phadtare and coworkers<sup>3</sup> have earlier reported the formation of 3-amino-2-methylquinazolin-4(3*H*)-one (**7**, R=CH<sub>3</sub>) in the reaction of 2-aminobenzoylhydrazine (**1a**) and ethyl acetoacetate in which they explained the formation of **7** (R=CH<sub>3</sub>) via a transient triazepinone intermediate. This reaction has now been extended to 2-methylaminobenzoylhydrazine (**1b**) with a view to isolating the pyrazolobenzotriazepinone, expected to be formed if the reaction were to follow the mechanism suggested by Phadtare and coworkers<sup>3</sup>. In ethanol/*p*-toluenesulfonic acid medium, **1b** reacted with ethyl

acetoacetate to form 1-(2'-methylaminobenzoyl)-3-methylpyrazolin-5-one (**8a**) as revealed by its IR, PMR and mass spectra (Table 2). The appearance of the methylene proton signal at δ 3.18 and the absence of =C-H signal in the PMR spectrum rules out the isomeric structure 1-(2'-methylaminobenzoyl)-5-methylpyrazolin-3-one (**9**). Also, **8a** underwent smooth dehydrative cyclisation in warm polyphosphoric acid ethyl ester to yield 2,4-dimethyl-9-oxopyrazolo[5,1-*b*]quinazoline (**10a**) (Scheme 2). Similar results were obtained when 2-ethylamino/benzylamino-benzoylhydrazines were reacted with ethyl benzoylacetate. Reaction with ethyl benzoylacetate, gave 2-phenyl-4-*H*-alkyl-9-oxopyrazolo[5,1-*b*]quinazolines (**11**) in one step (Scheme 2). Thus, 2-N-substituted-aminobenzoylhydrazines appear to react with β-ketoesters in a different way than that was suggested by Phadtare and coworkers<sup>3</sup> for 2-aminobenzoylhydrazine.

## Experimental Procedure

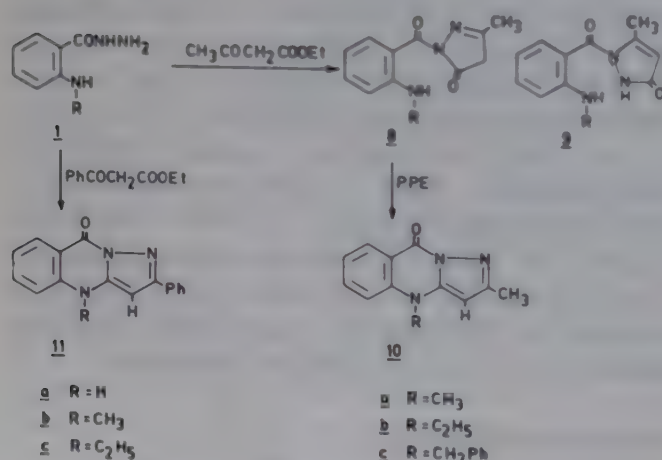
### 1-(2'-Amino/alkylaminobenzoyl)-3,6-dimethyl-1,2-dihydropyridazines (**2**): General procedure

A mixture of 2-amino/alkylaminobenzoylhydrazine (**1**, 1 mmol), hexan-2,5-dione (1 mmol) and

Table 2—Characterisation Data of 1-(2'-Alkylamino/aralkylaminobenzoyl)-3-methylpyrazolin-5-ones (**8**), 2-Methyl-4-alkyl/aralkyl-9-oxo-pyrazolo[5,1-*b*]quinazolines (**10**) and 2-Phenyl-4-*H*/alkyl-9-oxopyrazolo[5,1-*b*]quinazolines (**11**)

Compd	R	m.p. (°C)	Yield (%)	Mol. formula* (M <sup>+</sup> )	IR (cm <sup>-1</sup> )		PMR (δ ppm)			
					νC=O	νNH	Methyl	NH	Aromatic	Others
<b>8a</b>	CH <sub>3</sub>	242	83	C <sub>12</sub> H <sub>13</sub> N <sub>3</sub> O <sub>2</sub> (231)	1660 1720	3100	2.3 (s, 3H, =C-CH <sub>3</sub> ) 2.95 (s, 3H, N-CH <sub>3</sub> )	4.3 (s, 1H)	6.8-7.7 (m, 4H)	3.18 (s, 2H, CH <sub>2</sub> )
<b>8b</b>	C <sub>2</sub> H <sub>5</sub>	138	87	C <sub>13</sub> H <sub>15</sub> N <sub>3</sub> O <sub>2</sub> (245)	1660 1725	3130	1.06 (t, 3H, CH <sub>3</sub> ) 2.27 (s, 3H, =C-CH <sub>3</sub> ) 2.32 (s, 3H, =C-CH <sub>3</sub> )	4.88 (s, 1H)	6.7-7.75 (m, 4H)	3.03 (q, 2H, N-CH <sub>2</sub> ) 3.21 (s, 2H, CH <sub>2</sub> ) 3.3 (s, 2H, CH <sub>2</sub> ) 4.18 (s, 2H, CH <sub>2</sub> Ph)
<b>8c</b>	CH <sub>2</sub> C <sub>6</sub> H <sub>5</sub>	196	75	C <sub>18</sub> H <sub>17</sub> N <sub>3</sub> O <sub>2</sub> (307)	1660 1720	3170	2.48 (s, 3H, =C-CH <sub>3</sub> ) 3.58 (s, 3H, N-CH <sub>3</sub> ) 1.43 (t, 3H, CH <sub>3</sub> ) 2.45 (s, 3H, =C-CH <sub>3</sub> ) 2.42 (s, 3H, =C-CH <sub>3</sub> )	— —	7.12-8.5 (m, 4H)	5.96 (s, 1H, =CH)
<b>10a</b>	CH <sub>3</sub>	228	72	C <sub>12</sub> H <sub>11</sub> N <sub>3</sub> O (213)	1695	—	2.48 (s, 3H, =C-CH <sub>3</sub> ) 3.58 (s, 3H, N-CH <sub>3</sub> )	—	7.12-8.5 (m, 4H)	5.96 (s, 1H, =CH)
<b>10b</b>	C <sub>2</sub> H <sub>5</sub>	239	70	C <sub>13</sub> H <sub>13</sub> N <sub>3</sub> O (227)	1700	—	1.43 (t, 3H, CH <sub>3</sub> ) 2.45 (s, 3H, =C-CH <sub>3</sub> ) 2.42 (s, 3H, =C-CH <sub>3</sub> )	—	7.1-8.6 (m, 4H)	3.88 (q, 2H, N-CH <sub>2</sub> ) 6.05 (s, 1H, =CH)
<b>10c</b>	CH <sub>2</sub> C <sub>6</sub> H <sub>5</sub>	204	61	C <sub>18</sub> H <sub>15</sub> N <sub>3</sub> O (289)	1700	—	2.48 (s, 3H, =C-CH <sub>3</sub> ) 3.58 (s, 3H, N-CH <sub>3</sub> ) 1.43 (t, 3H, CH <sub>3</sub> ) 2.45 (s, 3H, =C-CH <sub>3</sub> ) 2.42 (s, 3H, =C-CH <sub>3</sub> )	—	6.5-8.6 (m, 9H)	4.54 (s, 2H, CH <sub>2</sub> Ph) 6.22 (s, 1H, =CH)
<b>11a</b>	H	300	86	C <sub>16</sub> H <sub>11</sub> N <sub>3</sub> O (261)	1705	—	—	—	—	—
<b>11b</b>	CH <sub>3</sub>	233	81	C <sub>17</sub> H <sub>13</sub> N <sub>3</sub> O (275)	1700	—	3.64 (s, 3H, N-CH <sub>3</sub> )	—	7.0-8.4 (m, 9H)	6.05 (s, 1H, =CH)
<b>11c</b>	C <sub>2</sub> H <sub>5</sub>	208	80	C <sub>18</sub> H <sub>15</sub> N <sub>3</sub> O (289)	1705	—	1.5 (t, 3H, CH <sub>3</sub> )	—	7.1-8.5 (m, 9H)	4.14 (q, 2H, N-CH <sub>2</sub> ) 6.27 (s, 1H, =CH)

\*Satisfactory analytical data were obtained: C, ±0.042; H, ±0.02; N, ±0.037.



Scheme 2

the homogenous solution was filtered, recrystallised from methanol, and characterised as **2** (Table 1).

#### 1-(2'-Amino/alkylaminobenzoylamino)-2,5-dimethylpyrroles (**3**): General procedure

A mixture of **1** (1 mmol), hexan-2,5-dione (1 mmol) and *p*-toluenesulfonic acid (20 mg) was refluxed in ethanol (20 ml) for 15 min. The reaction mixture was cooled, the excess solvent removed under reduced pressure and the residue washed with water (10 ml) and recrystallised from pet ether (60-80°)-benzene to colourless crystals of **3** (Table 1).

#### Reaction of **1** with hexan-2,5-dione: General procedure

To an ethanolic solution of **1** (10 mmol in 15 ml), hexan-2,5-dione (10 mmol) was added. After refluxing the mixture for 30 min, the reaction mix-

triethylamine (10 ml) was refluxed on a steam-bath for 15 min. The product that separated out from

ture was cooled and ethanol removed under reduced pressure. The resulting brown solid was chromatographed over a column of neutral alumina (120-200 mesh) using benzene and ethyl acetate as eluents. **3** were isolated (41-47%) from benzene (3 × 15 ml) and **2** (32-35%) from ethyl acetate (3 × 15 ml) fractions.

### 3-(2',5'-Dimethylpyrrolo)quinazolin-4(3*H*)-one (**6**):

*Method (i)*—From 1-(2'-aminobenzoyl)-3,6-dimethyl-1,2-dihydropyridazine (**2a**)

**2a** (230 mg) was refluxed in ethyl formate (5 ml) for 8 hr. The excess solvent was distilled off and the residue recrystallised from pet ether (60-80°) to give **6**, m.p. 89°; yield 72% (Found: C, 70.34; H, 5.41; N, 17.53. Calculated: C, 70.29; H, 5.44; N, 17.57%).

*Method (ii)*—From 1-(2'-aminobenzoylamino)-2,5-dimethylpyrrole (**3a**)

**3a** (230 mg) was refluxed in ethyl formate (5 ml) for 8 hr. Ethyl formate was distilled off and the residue was recrystallised from pet ether (60-80°) to afford **6**, m.p. and m.m.p. 89°; yield 86%.

*Method (iii)*—From 3-aminoquinazolin-4(3*H*)-one

A mixture of 3-aminoquinazolin-4(3*H*)-one (160 mg), hexan-2,5-dione (.115 ml) and *p*-toluenesulfonic acid (20 mg) was refluxed in ethanol (10 ml) for 1 hr. The excess solvent was distilled off and the brown residue was recrystallised from pet ether (60-80°) to give **6**, m.p. and m.m.p. 88°; yield 80%.

1-(2'-Alkylamino/aralkylaminobenzoyl)-3-methylpyrazolin-5-ones (**8**): *General Procedure*

A mixture of **1** (1 mmol), ethyl acetoacetate (1

mmol) and *p*-toluenesulfonic acid was refluxed in ethanol (10 ml) for 10 hr. Compound **8** that separated out from the cooled solution was filtered and recrystallised from ethanol (Table 2).

2-Methyl-4-alkyl/aralkyl-9-oxo-pyrazolo[5,1-*b*]quinazolines (**10**): *General procedure*

A solution of **8** (1 mmol) in polyphosphoric acid ethyl ester (5 ml) was heated at steam-bath temperature for 6 hr. The reaction mixture was added to water (50 ml) and the solution neutralised with liquor ammonia. The precipitate was washed with water (5 × 20 ml) and recrystallised from benzene (Table 2).

2-Phenyl-4-*H*/alkyl-9-oxo-pyrazolo[5,1-*b*]quinazolines (**11**)

A mixture of **1** (1 mmol), ethyl benzoylacetate (1 mmol) and *p*-toluenesulfonic acid (20 mg) was refluxed in ethanol (10 ml) for 8 hr. Compound **11** that separated out on cooling the reaction mixture was filtered and recrystallised from methanol (Table 2).

### Acknowledgement

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# Heterocyclic Systems Containing Bridgehead Nitrogen Atom: Synthesis of Thiazolo [3', 2': 2, 3][1, 2, 4] triazino [5, 6-*b*] indoles & Isomeric Thiazolo [2', 3': 3, 4][1, 2, 4] triazino [5, 6-*b*] indoles

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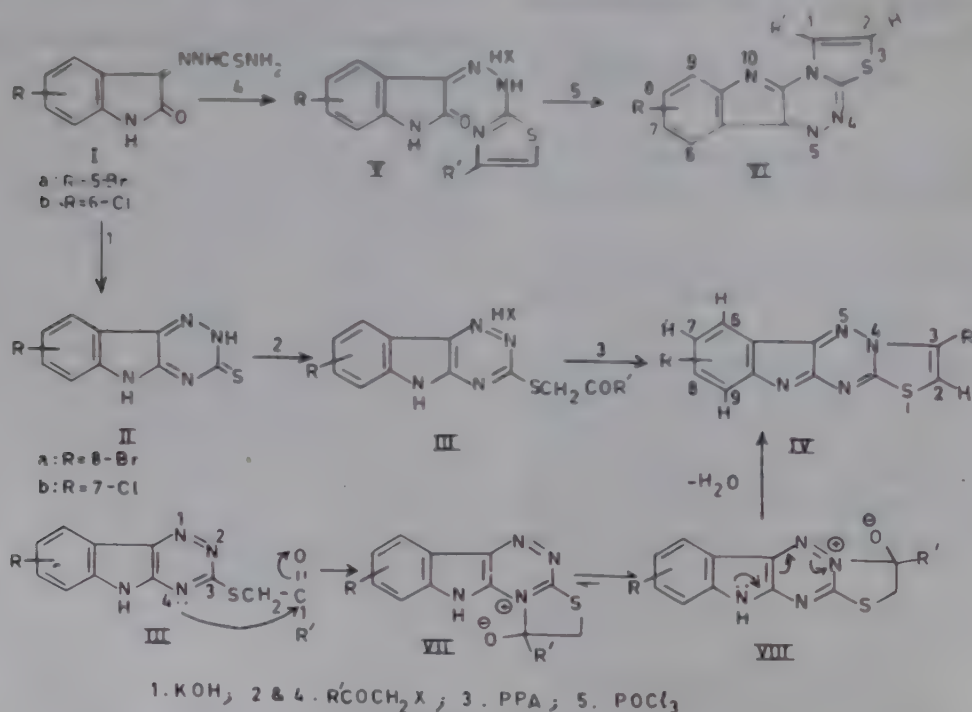
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8-Bromo-and 7-chloro-5*H*-2, 3-dihydro [1, 2, 4] triazino [5, 6 *b*] indole-3-thiones (II) on condensation with  $\alpha$ -halogenoketones give 5*H*-3-arylmethylthio-8-bromo- and 5*H*-3-arylmethylthio-7-chloro [1, 2, 4] triazino [5, 6-*b*] indole hydrohalides (III) which undergo PPA cyclization to furnish 3-aryl-7-bromo- and 3-aryl-8-chloro-thiazolo [3', 2': 2, 3][1, 2, 4] triazino [5, 6-*b*] indoles (IV) and not the angular isomeric 1-aryl-7-bromo-and 1-aryl-8-chloro-thiazolo [2', 3': 3, 4][1, 2, 4] triazino [5, 6 *b*] indoles (VI). The unequivocal synthesis of the latter (VI) has also been accomplished.

In continuation of our earlier studies<sup>1-3</sup> on the orientation of cyclization in the reaction of unsymmetrical mercaptoazoles with bifunctional compounds, we wish to report herein the results of our study on the reaction of unsymmetrical azines (mercaptoindole-triazines) with  $\alpha$ -halogenoketones.

8-Bromo-5*H*-2, 3-dihydro[1, 2, 4]triazino [5, 6-*b*]indole-3-thione (IIa), obtained by the condensation of 5-bromoisatin with thiosemicarbazide followed by cyclization of the intermediate 5-bromoisatin-3-thiosemicarbazone (Ia) with alkali, when condensed with  $\alpha$ -halogenoketones gave 5*H*-3-arylmethylthio-8-bromo[1, 2, 4]triazino[5, 6-*b*] indole hydrohalides (IIIa-c). The ketones IIIa-c being unsymmetrical, on cycli-

zation with PPA were expected to form 3-aryl-7-bromothiazolo[3', 2': 2, 3][1, 2, 4] triazino[5, 6-*b*] indoles (IVa-c) or 1-aryl-7-bromothiazolo[2', 3': 3, 4][1, 2, 4] triazino[5, 6-*b*] indoles (VIa-c) or both depending upon the mode of cyclization. However, cyclization of III gave a single product (TLC) and it was confirmed by IR and PMR spectral data. The ketones III exhibited a band at 1670-1705 cm<sup>-1</sup> due to C=O function, whereas the absence of this band in the products (IV) showed the absence of carbonyl group, thereby suggesting the cyclic structure for IV. The signal at  $\delta$ 7.80 (1H, *s*, C<sub>2</sub>-H) in the PMR spectrum of IVa corroborated the cyclic structure. However, the spectral data were not of much help in deciding either



SCHEME 1

the linear structure IV or the angular structure VI for the product.

A similar sequence of reactions starting from 6-chloroisatin-3-thiosemicarbazone (Ib) furnished 3-aryl-8-chlorothiazolo[3', 2': 2, 3][1, 2, 4]triazino[5, 6-*b*]indoles (IVd-g) (Scheme 1).

The mode of cyclization in III will be governed by the stability of the cyclic transition state (VII or VIII). In structure III, N-4 being more nucleophilic than N-2 (as N-2 is attached to N-1) will attack the carbonyl carbon of the ketone moiety giving VII. There exists a steric repulsion between NH of the pyrrole ring and aryl moiety of the ketosulphide chain in VII and this crowding would render the transition state VII completely unstable. Thus, the initially formed intermediate (VII) being energetically more active, opens up and closes at N-2 to give energetically less active intermediate VIII in which there would be no such steric crowding. The intermediate VIII finally undergoes prototropic change followed by loss of a water molecule to give IV.

The unequivocal synthesis of the angular isomer (VI) was achieved by condensing 5-bromo- or 6-chloro-isatin-3-thiosemicarbazone (Ia or Ib) with  $\alpha$ -halogenoketones followed by cyclization of the resulting 5-bromo- or 6-chloro-isatin-3-(4-aryl-2-thiazolyl) hydrazone hydrohalides (Va-h) with POCl<sub>3</sub> to furnish 1-aryl-7-bromo- or 1-aryl-8-chloro-thiazolo[2', 3': 3, 4][1, 2, 4]triazino[5, 6-*b*]indoles (VIa-h). The amide carbonyl ( $>\text{N}-\overset{\text{I}}{\text{C}}=\text{O}$ ) absorption, observed at 1680-1685 cm<sup>-1</sup> in V, was found to be absent in the IR spectra of VI. The PMR spectra (*vide experimental*) corroborated the cyclic structure for VI.

### Experimental Procedure

Melting points are uncorrected. TLC was performed on silica-gel plates using acetone-benzene (1:3) as irrigant. IR spectra in nujol or KBr were recorded on a Beckman IR-20 spectrophotometer ( $\nu_{\text{max}}$  in cm<sup>-1</sup>) and PMR spectra on a Jeol-FT 90 MHz spectrometer using TMS as internal standard (Chemical shift in  $\delta$ , ppm).

#### 5-Bromoisatin-3-thiosemicarbazone (Ia)

A mixture of 5-bromoisatin (11.3g, 0.05 mol) in acetic acid (80 ml) and thiosemicarbazide (5.0g, 0.055 mol) in water (50 ml) was heated under reflux on a heating mantle for half an hour when a yellow solid separated out. It was filtered, washed well with water and crystallised from ethanol-DMF furnishing Ia as golden yellow needles, yield 12.5g (84%), m.p. 265° (d) (Found: N, 19.1; S, 11.3. C<sub>9</sub>H<sub>7</sub>N<sub>4</sub>OSBr requires N, 18.7; S, 10.7%; IR: 1130 (C=S), 1600 (C=N), 1680 (C=O), 3150, 3275, 3400 (NH, NH<sub>2</sub>).

A similar reaction on 6-chloroisatin gave 6-chloroisatin-3-thiosemicarbazone (Ib) yield 59%, m.p. >280° (Found: N, 21.8; S, 12.3. C<sub>9</sub>H<sub>7</sub>N<sub>4</sub>OSCl requires N, 22.0; S, 12.6%; IR: 1140 (C=S), 1600 (C=N), 1690 (C=O), 3130, 3380, 3480 (NH, NH<sub>2</sub>).

#### 8-Bromo-5H-2, 3-dihydro[1,2,4]triazino[5,6-*b*]indole-3-thione (IIa)

5-Bromoisatin-3-thiosemicarbazone (Ia, 8.97g, 0.03 mol) in 4% KOH (200 ml) was heated under reflux for 4 hr. The reaction mixture was cooled and the insoluble material removed by filtration. The filtrate on neutralization with dil. HCl gave an orange solid which was filtered, washed well with water and crystallized from aq. DMF furnishing IIa as yellow needles, yield 4.70 g (56%), m.p. >300° (Found: N, 20.6; S, 11.9. C<sub>9</sub>H<sub>5</sub>N<sub>4</sub>SBr requires N, 19.9; S, 11.4%; IR: 1160 (C=S), 1585 (C-N), 1610 (C=N), 3190 (N-H).

A similar reaction on Ib (7.62 g) gave 7-chloro-5H-2, 3-dihydro[1, 2, 4]triazino[5, 6-*b*]indole-3-thione (IIb), yield 3.0 g (42%), m.p. >280° (Found: N, 24.2; S, 13.9. C<sub>9</sub>H<sub>5</sub>N<sub>4</sub>SCl requires N, 23.7; S, 13.5%; IR: 1140 (C=S), 1570 (C-N), 1600 (C=N), 3290 (N-H).

#### 5H-3-(*p*-Chlorophenacylthio)-8-bromo [1,2,4]triazino [5,6-*b*]indole hydrobromide (IIIa)

A mixture of IIa (1.405g, 0.005 mol) and *p*-chlorophenacyl bromide (1.17g, 0.005 mol) in DMF (80 ml) was heated under reflux on a heating mantle for 3 hr, cooled to room temperature and poured into ice water. The solid, thus obtained, was washed with water and crystallized from aq. DMF to give IIIa as yellow needles, yield 1.4 g (51%), m.p. >300° (Found: N, 11.4; S, 6.9. C<sub>11</sub>H<sub>11</sub>N<sub>4</sub>OSBr<sub>2</sub>Cl requires N, 10.9; S, 6.2%; IR: 1570 (C-N), 1590, 1610 (C=N), 1680 (C=O), 3200 (N-H).

Following members of the series were also prepared in a similar way.

IIIb (R=8-Br; R'=p-Br-C<sub>6</sub>H<sub>4</sub>-): Yield 57%, m.p. >300° (Found: N, 10.7; S, 6.2. C<sub>17</sub>H<sub>11</sub>N<sub>4</sub>OSBr<sub>3</sub> requires N, 10.0; S, 5.7%; IR: 1575 (C-N), 1600 (C=N), 1670 (C=O), 3175 (N-H).

IIIc (R=8-Br; R'=p-CH<sub>3</sub>-C<sub>6</sub>H<sub>4</sub>-): Yield (53%), m.p. >300° (Found: N, 10.8; S, 6.1. C<sub>18</sub>H<sub>14</sub>N<sub>4</sub>OSBr<sub>2</sub> requires N, 11.3; S, 6.5%; IR: 1570 (C-N), 1605 (C=N), 1675 (C=O), 3220 (N-H).

IIId (R=7-Cl; R'=p-Br-C<sub>6</sub>H<sub>4</sub>-): Yield (54%), m.p. >280° (Found: N, 11.4; S, 6.8. C<sub>17</sub>H<sub>11</sub>N<sub>4</sub>OSBr<sub>2</sub>Cl requires N, 10.9; S, 6.2%; IR: 1575 (C-N), 1600 (C=N), 1675 (C=O), 3300 (N-H).

IIIe (R=7-Cl; R'=C<sub>6</sub>H<sub>5</sub>-): Yield (50%), m.p. 150° (Found: N, 14.9; S, 8.7. C<sub>17</sub>H<sub>12</sub>N<sub>4</sub>SOCl<sub>2</sub> requires N, 14.3; S, 8.2%; IR: 1585 (C-N), 1620 (C=N), 1670 (C=O), 3275 (N-H).

III<sub>f</sub> (R=7-Cl; R'=p-Cl-C<sub>6</sub>H<sub>4</sub>-): Yield 52%, m.p. 240° (Found: N, 12.3; S, 6.4. C<sub>17</sub>H<sub>11</sub>N<sub>4</sub>BrSOCl<sub>2</sub> requires N, 11.9; S, 6.8%); IR: 1520 (C—N), 1585, 1600 (C=N), 1675 (C=O), 3290 (N—H).

III<sub>g</sub> (R=7-Cl; R'=p-C<sub>6</sub>H<sub>5</sub>-C<sub>6</sub>H<sub>4</sub>-): Yield 45%, m.p. 210° (Found: N, 10.6; S, 5.9. C<sub>23</sub>H<sub>16</sub>N<sub>4</sub>BrSOCl requires N, 10.9; S, 6.3%); IR: 1515 (C—N), 1580 (C=N), 1680 (C=O), 3450 (N—H).

**7-Bromo-3-(p-chlorophenyl)thiazolo[3', 2': 2, 3][1, 2, 4]triazino[5, 6-b]indole (IV<sub>a</sub>)**

Ketone III<sub>a</sub> (1.0 g) in a mixture of H<sub>3</sub>PO<sub>4</sub> (3.0 ml) and P<sub>2</sub>O<sub>5</sub> (4.0 g) was heated in an oil-bath at 150° for 3 hr. The reaction mixture was cooled to room temperature, poured into water and neutralized with aq. K<sub>2</sub>CO<sub>3</sub> solution. The solid, thus obtained, was filtered, washed well with water and crystallised from DMF to IV<sub>a</sub> as pink granules, yield 0.35 g (47%), m.p. >300° (Found: C, 48.8; H, 1.7; N, 13.6; S, 8.1. C<sub>17</sub>H<sub>8</sub>N<sub>4</sub>SBrCl requires C, 49.1; H, 1.9; N, 13.5; S, 7.7%); IR: 1520 (C—N), 1600 (C=N); PMR (TFA): 7.78 (4H, *q*, *J*=9 Hz, *p*-chlorophenyl protons), 7.80 (1H, *s*, C<sub>2</sub>-H), 8.07 (1H, *d*, *J*=9 Hz, C<sub>9</sub>-H), 8.13 [1H, *dd*, C<sub>8</sub>-H, *J*<sub>6,8</sub>=3 Hz (*meta*-coupling), *J*<sub>8,9</sub>=9 Hz (*ortho*-coupling)], 8.55 (1H, *d*, *J*=3 Hz, C<sub>6</sub>-H).

Following members of the series were also prepared in a similar way.

IV<sub>b</sub> (R=7-Br; R'=p-Br-C<sub>6</sub>H<sub>4</sub>-): Yield 43%, m.p. >300° (Found: N, 12.9; S, 7.5. C<sub>17</sub>H<sub>8</sub>N<sub>4</sub>SBr<sub>2</sub> requires N, 12.2; S, 7.0%); IR: 1520 (C—N), 1625 (C=N).

IV<sub>c</sub> (R=7-Br; R'=p-CH<sub>3</sub>-C<sub>6</sub>H<sub>4</sub>-): Yield 50%, m.p. >300° (Found: N, 14.7; S, 7.5. C<sub>18</sub>H<sub>11</sub>N<sub>4</sub>SBr requires N, 14.2; S, 8.1%); IR: 1520 (C—N), 1610 (C=N).

IV<sub>d</sub> (R=8-Cl; R'=p-Br-C<sub>6</sub>H<sub>4</sub>-): Yield 56%, m.p. >280° (Found: C, 49.7; H, 1.6; N, 13.8; S, 7.2. C<sub>17</sub>H<sub>8</sub>N<sub>4</sub>SBrCl requires C, 49.1; H, 1.9; N, 13.5; S, 7.7%); IR: 1525 (C—N), 1610 (C=N); PMR (TFA): 7.68 (1H, *d*, *J*=8.1 Hz, C<sub>6</sub>-H), 7.87 (1H, *s*, C<sub>2</sub>-H), 7.79 [1H, *dd*, C<sub>7</sub>-H, *J*<sub>7,9</sub>=1.5 Hz (*meta*-coupling), *J*<sub>6,7</sub>=8.1 Hz (*ortho*-coupling)], 7.91 (4H, *q*, *J*=8.1 Hz, *p*-bromophenyl protons), 8.13 (1H, *d*, *J*=1.5 Hz, C<sub>9</sub>-H).

IV<sub>e</sub> (R=8-Cl; R'=C<sub>6</sub>H<sub>5</sub>-): Yield 50%, m.p. 230° (Found: N, 17.1; S, 9.6. C<sub>17</sub>H<sub>9</sub>N<sub>4</sub>SCl requires N, 16.6; S, 9.5%); IR: 1525 (C—N), 1635 (C=N).

IV<sub>f</sub> (R=8-Cl; R'=p-Cl-C<sub>6</sub>H<sub>4</sub>-): yield 49%, m.p. >280° (Found: N, 14.8; S, 8.2. C<sub>17</sub>H<sub>8</sub>N<sub>4</sub>SCl<sub>2</sub> requires N, 15.1; S, 8.6%); IR: 1525 (C—N), 1610 (C=N).

IV<sub>g</sub> (R=8-Cl; R'=p-C<sub>6</sub>H<sub>4</sub>-C<sub>6</sub>H<sub>4</sub>-): Yield 40%, m.p. >280° (Found: N, 13.2; S, 7.5. C<sub>23</sub>H<sub>13</sub>N<sub>4</sub>SCl requires N, 13.6; S, 7.8%); IR: 1520 (C—N), 1600 (C=N).

**5-Bromoisatin-3 (4-p-chlorophenyl-2-thiazolyl) hydrazone hydrobromide (V<sub>a</sub>)**

A mixture of Ia (1.495 g, 0.005 mol) and *p*-chlorophenacyl bromide (1.17 g, 0.005 mol) in anhyd.

ethanol (25 ml) and DMF (25 ml) was heated under reflux on a heating mantle for 3 hr when an orange yellow solid separated out. The reaction mixture was cooled to room temperature and the solid filtered, washed well with water and crystallized from DMF-water to give V<sub>a</sub> as bright yellow flakes, yield 1.8 g (70%), m.p. >300° (Found: N, 11.7; S, 6.6. C<sub>17</sub>H<sub>11</sub>N<sub>4</sub>OSBr<sub>2</sub>Cl requires N, 10.9; S, 6.2%); IR: 1540 (C—N), 1610 (C=N), 1680 (C=O), 3100 (N—H).

Following members of the series were also prepared in a similar way.

V<sub>b</sub> (R=5-Br; R'=p-Br-C<sub>6</sub>H<sub>4</sub>-): Yield 64%, m.p. >300° (Found: N, 10.6; S, 5.2. C<sub>17</sub>H<sub>11</sub>N<sub>4</sub>OSBr<sub>3</sub> requires N, 10.0; S, 5.7%); IR: 1540 (C—N), 1610 (C=N), 1680 (C=O), 3150 (N—H).

V<sub>c</sub> (R=5-Br; R'=p-CH<sub>3</sub>-C<sub>6</sub>H<sub>4</sub>-): Yield 68%, m.p. >300° (Found: N, 11.8; S, 7.1. C<sub>18</sub>H<sub>14</sub>N<sub>4</sub>OSBr<sub>2</sub> requires N, 11.3; S, 6.5%); IR: 1550 (C—N), 1625 (C=N), 1685 (C=O), 3100 3150 (N—H).

V<sub>d</sub> (R=5-Br; R'=p-C<sub>6</sub>H<sub>5</sub>-C<sub>6</sub>H<sub>4</sub>-): Yield 65%, m.p. >300° (Found: N, 10.7; S, 6.4. C<sub>23</sub>H<sub>16</sub>N<sub>4</sub>OSBr<sub>2</sub> requires N, 10.1; S, 5.8%); IR: 1545 (C—N), 1610 (C=N), 1675 (C=O), 3150 (N—H).

V<sub>e</sub> (R=6-Cl; R'=p-Br-C<sub>6</sub>H<sub>4</sub>-): Yield 58%, m.p. >280° (Found: N, 11.2; S, 6.8. C<sub>17</sub>H<sub>11</sub>N<sub>4</sub>OSBr<sub>2</sub>Cl requires N, 10.9; S, 6.2%); IR: 1530 (C—S), 1615 (C=N), 1685 (C=O), 3175 (N—H).

V<sub>f</sub> (R=6-Cl; R'=C<sub>6</sub>H<sub>5</sub>-): Yield 58%, m.p. 275° (Found: N, 14.0; S, 8.1. C<sub>17</sub>H<sub>12</sub>N<sub>4</sub>SOCl<sub>2</sub> requires N, 14.4; S, 8.2%); IR: 1530 (C—N), 1610 (C=N), 1675 (C=O), 3180 (N—H).

V<sub>g</sub> (R=6-Cl; R'=p-Cl-C<sub>6</sub>H<sub>4</sub>-): Yield 62%, m.p. >280° (Found: N, 12.3; S, 6.3. C<sub>17</sub>H<sub>11</sub>N<sub>4</sub>SOCl<sub>2</sub>Br requires N, 11.9; S, 6.8%); IR: 1530 (C—N), 1615 (C=N), 1685 (C=O), 3175 (N—H).

V<sub>h</sub> (R=6-Cl; R'=p-C<sub>6</sub>H<sub>5</sub>-C<sub>6</sub>H<sub>4</sub>-): Yield 48%, m.p. >280° (Found: N, 11.6; S, 6.8. C<sub>23</sub>H<sub>16</sub>N<sub>4</sub>SOCIBr requires N, 11.0; S, 6.3%); IR: 1525 (C—N), 1605 (C=N), 1670 (C=O), 3175 (N—H).

**1-(p-Chlorophenyl)-7-bromothiazolo[2', 3': 3, 4][1, 2, 4]triazino[5, 6-b]indole (VI<sub>a</sub>)**

Compound V<sub>a</sub> (1.0 g) in POCl<sub>3</sub> (10.0 ml) was heated in an oil-bath at 125° for 3 hr. The reaction mixture was cooled to room temperature, poured into cold water and neutralized with K<sub>2</sub>CO<sub>3</sub> solution. The solid, thus obtained, was filtered, washed well with water and crystallised from DMF to furnish V<sub>a</sub> as orange-red needles, yield 0.45 g (56%), m.p. >300° (Found: C, 49.6; H, 2.1; N, 14.0; S, 7.3. C<sub>17</sub>H<sub>8</sub>N<sub>4</sub>SBrCl requires C, 49.1; H, 1.9; N, 13.5; S, 7.7%); IR: 1580 (C—N), 1600 (C=N), PMR (TFA): 7.56 (1H, *d*, *J*=9 Hz, C<sub>9</sub>-H) 7.76 (4H, degenerate *q*, *p*-chlorophenyl protons), 8.05 [1H, *dd*, C<sub>8</sub>-H, *J*<sub>6,8</sub>=3 Hz (*meta*-coupling), *J*<sub>8,9</sub>=9 Hz (*ortho*-

coupling)], 8.40 (1H, *s*, C<sub>2</sub>-H), 8.79 (1H, *d*  $J=3$ Hz, C<sub>6</sub>-H).

Following members of the series were also prepared in a similar way.

VIb (R=7-Br; R'=p-Br-C<sub>6</sub>H<sub>4</sub>-): Yield 61%, m.p. >300° (Found: N, 12.6; S, 6.5. C<sub>17</sub>H<sub>8</sub>N<sub>4</sub>SBr<sub>2</sub> requires N, 12.2; S, 7.0%); IR: 1575 (C—N), 1590, 1600 (C=N).

VIc (R=7-Br; R'=p-CH<sub>3</sub>C<sub>6</sub>H<sub>4</sub>-): Yield 54%, m.p. >300° (Found: N, 14.8; S, 8.7. C<sub>18</sub>H<sub>11</sub>N<sub>4</sub>SBr requires N, 14.2; S, 8.1%); IR: 1540 (C—N), 1615 (C=N).

VI d (R=7-Br; R'=p-C<sub>6</sub>H<sub>5</sub>-C<sub>6</sub>H<sub>4</sub>-): Yield 52%, m.p. >300° (Found: N, 12.0; S, 7.5. C<sub>23</sub>H<sub>13</sub>N<sub>4</sub>SBr requires N, 12.3; S, 7.0%); IR: 1575 (C—N), 1645 (C=N).

VIe (R=8-Cl; R'=p-Br-C<sub>6</sub>H<sub>4</sub>-): Yield 52%, m.p. >280° (Found: C, 48.8; H, 2.1. N, 13.2; S, 8.2; C<sub>17</sub>H<sub>8</sub>N<sub>4</sub>SClBr requires C, 49.1; H, 1.9; N, 13.5; S, 7.7%); IR: 1540 (C—N), 1615 (C=N); PMR (TFA): 7.11 (1H, *d*,  $J=8.1$ Hz, C<sub>6</sub>-H), 7.44 (4H, *q*,  $J=8.1$ Hz, *p*-bromophenyl protons), 7.48 [1H, *dd*, C<sub>7</sub>-H,  $J_{7,9}=1.5$ Hz (*meta*-coupling),  $J_{6,7}=8.1$  Hz (*ortho*-coupling)], 7.72 (1H, *s*, C<sub>2</sub>-H), 7.81 (1H, *d*,  $J=1.5$  Hz, C<sub>9</sub>-H).

VI f (R=8-Cl; R'=C<sub>6</sub>H<sub>5</sub>-): Yield 55%, m.p. >280°

(Found: N, 16.1; S, 9.9. C<sub>17</sub>H<sub>9</sub>N<sub>4</sub>SCl requires N, 16.6; S, 9.5%); IR: 1525 (C—N), 1585, 1610 (C=N).

VIg (R=8-Cl; R'=p-Cl-C<sub>6</sub>H<sub>4</sub>-): Yield 52%, m.p. >280° (Found: N, 15.6; S, 8.4. C<sub>17</sub>H<sub>8</sub>N<sub>4</sub>SCl<sub>2</sub> requires N, 15.1; S, 8.6%); IR: 1540 (C—N), 1615 (C=N).

VIh (R=8-Cl; R'=p-C<sub>6</sub>H<sub>5</sub>-C<sub>6</sub>H<sub>4</sub>-): Yield 38%, m.p. >280° (Found: N, 13.8; S, 7.3. C<sub>23</sub>H<sub>13</sub>N<sub>4</sub>SCl requires N, 13.6; S, 7.8%); IR: 1525 (C—N), 1620 (C=N).

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## Notes

### A New Simple Synthesis of (Z)-7-Nonadecen-11-one & 7-Eicosen-11-one, Pheromone Components of Peach Fruit Moth (*Corposina niponensis* Walsingham)

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The title pheromone components IIa and IIb of Japanese peach fruit moth, have been synthesised in two-steps via regioselective alkylation of appropriate metallohydrazones followed by hydrolysis.

(Z)-7-Nonadecen-11-one (IIa) and (Z)-7-Eicosen-11-one (IIb) have been recognised as the potent male attractants of Japanese peach fruit moth, *Corposina niponensis* Walsingham<sup>1</sup>, and a variety of synthetic methods have been reported<sup>1-9</sup>. In continuation of our interest<sup>10</sup> in the synthesis of insect pheromones, we herein report a convenient two-step synthesis of IIa and IIb in 70.6 and 74% overall yields respectively.

Construction of carbon-carbon bond regioselectively via  $\alpha$ -lithio-N,N-dimethylhydrazones has been well documented in literature<sup>11</sup>. In the present approach, this is used as a key step towards IIa and IIb. Thus treatment of  $\alpha$ -lithioacetone dimethylhydrazone with 7-(bromo)-2(Z)-nonene<sup>12</sup> followed by alkylation with 1-bromoheptane and 1-bromooctane led to the corresponding hydrazones (Ia) and (Ib). Oxidative hydrolysis<sup>13</sup> of Ia, b with aq. NaIO<sub>4</sub> at pH 7 and 20-25° using methanol as cosolvent afforded the desired IIa and IIb respectively in high yields (Chart 1).

#### (Z)-7-Nonadecen-11-one dimethylhydrazone (Ia)

Acetone dimethylhydrazone (1.12 g, 11.2 mmol) in dry THF (20 ml), under N<sub>2</sub> atmosphere, was metallated with LDA (12.4 mmol) in THF (15 ml) (LDA was

freshly prepared from diisopropylamine and 1.7 N *n*-Buli) at 0° for 2 hr. The reaction solution was cooled to -78°C and treated with 1-bromo-2(Z)-nonene (2.52 g, 12.4 mmol) in THF (10 ml). After keeping the reaction mixture for 1 hr at -78° and for 20 hr at 0° (TLC monitoring), the resulting solution was treated with freshly prepared LDA (12.4 mmol) in THF (10 ml) followed by addition of 1-bromoheptane (2.0 g, 11.06 mmol) in THF (10 ml). The reaction mixture was kept for 1 hr at -78°, and for 20 hr at 0°. It was poured into water-dichloromethane (3:1), extracted with dichloromethane and the organic extract dried. Solvent evaporation followed by distillation under reduced pressure afforded Ia (2.16 g, 72%); b.p. 140°/8-10 mm; IR (thin film): 1650; PMR(CCl<sub>4</sub>):  $\delta$  5.65-5.30 (*m*, 2H, protons at C-7 and C-8), 2.3-2.0 [*s+m*, 14H, =NN(CH<sub>3</sub>)<sub>2</sub> and methylene protons at C-6, C-9, C-10 and C-12], 1.33 (*bs*, 20H, methylene protons at C<sub>2</sub>-C<sub>5</sub> and C<sub>13</sub>-C<sub>18</sub>), 0.87 (*t*, 6H, -CH<sub>3</sub> at C-1 and C-19) (Found: C, 78.4; H, 13.1. C<sub>21</sub>H<sub>42</sub>N<sub>2</sub> requires C, 78.2; H, 13.0%).

#### (Z)-7-Eicosen-11-one dimethylhydrazone (Ib)

It was prepared from acetone dimethylhydrazone (1.12 g, 11.2 mmol), LDA (12.4 mmol), 1-bromo-2(Z)-nonene (2.52 g, 12.4 mmol), LDA (12.4 mmol) and 1-bromooctane (2.14 g, 11.06 mmol) in THF as described above; yield 2.63 g (78%); b.p. 160-62°/8-10 mm; IR (thin film): 1650; PMR (CCl<sub>4</sub>):  $\delta$  5.60-5.30 (*m*, 2H, protons at C-7 and C-8), 2.3-2.0 [*s+m*, 14H, =NN(CH<sub>3</sub>)<sub>2</sub> and methylene protons at C-6, C-9, C-10 and C-12], 1.35 (*bs*, 22H, methylene protons at C<sub>2</sub>-C<sub>5</sub> and C<sub>13</sub>-C<sub>19</sub>), 0.87 (*t*, 6H, CH<sub>3</sub> at C-1 and C-20) (Found: C, 78.5; H, 13.2. C<sub>22</sub>H<sub>44</sub>N<sub>2</sub> requires 78.6; H, 13.0%).

#### (Z)-7-Nonadecen-11-one (IIa) and 7-eicosen-11-one (IIb)

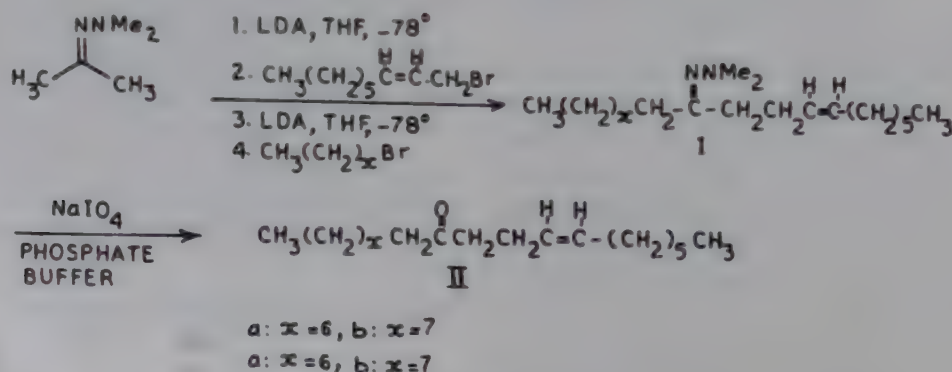


CHART 1

Compound (Ia/Ib, 1.2 g, 4 mmol) was dissolved in methanol (60 ml) and phosphate buffer (pH 7, 12 ml). To this was added a solution of sodium periodate (3.546 g) in water (20 ml) at 25° with stirring. Gas evolution and precipitation of sodium iodate ensued rapidly. After completion of hydrolysis (TLC monitoring), the reaction mixture was filtered, diluted with water extracted with dichloromethane and the organic layer dried. Evaporation of the solvent under reduced pressure followed by column chromatography over silica gel using pet. ether as eluent afforded IIa (1.098 g, 98%)/IIb (0.93 g, 95%).

IIa—IR (thin film): 2935, 2890, 1710, 1650, 720  $\text{cm}^{-1}$ ; PMR ( $\text{CCl}_4$ ):  $\delta$  5.5-5.30 (*m*, 2H, proton at C-7 and C-8), 2.3-2.0 (*m+s*, 8H, methylene protons at C-6, C-9, C-10, C-12), 1.35 (*bs*, 20H, methylene protons at  $\text{C}_2\text{—C}_5$ , 0.87 (*t*, 6H,  $\text{—CH}_3$  at C-1 and C-19) (Found: C, 81.3; H, 12.9.  $\text{C}_{19}\text{H}_{36}\text{O}$  requires C, 81.4, H, 12.8%).

IIb—IR (thin film): 2935, 2880, 1715, 725  $\text{cm}^{-1}$ ; PMR ( $\text{CCl}_4$ ):  $\delta$  5.4-5.25 (*m*, 2H, proton at C-7 and C-8), 2.3-2.0 (*m+s*, 8H, methylene protons at  $\text{C}_2\text{—C}_5$  and  $\text{C}_{13}\text{—C}_{18}$ ), 0.87 (*t*, 6H,  $\text{—CH}_3$  at C-1 and C-20) (Found: C, 81.50; H, 13.0.  $\text{C}_{20}\text{H}_{38}\text{O}$  requires C, 81.6;

H, 13.1%).

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## Synthesis of 2-(*o*-Hydroxyphenyl)- 5, 6-benzo-1, 3-oxazine

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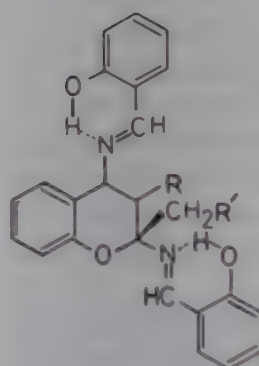
Reaction of salicylaldehyde with ammonium acetate in ethanol at 0-5°C produces 2-(*o*-hydroxyphenyl)-5, 6-benzo-1, 3-oxazine (**4**) in 23-25% yield in 15-18 hr.

Condensation of salicylaldehyde with carbonyl compounds in the presence of ammonium acetate has been reported to yield benzopyran derivatives (e.g. **1**)<sup>1</sup>. Shanmugam and coworkers<sup>2</sup>, on the other hand, obtained compound **2** from salicylaldehyde by reaction with ammonium acetate in acetic acid. A compound of interest in this connection is **3** the nitrogen analogue of **2**<sup>3</sup>.

Now we have found that salicylaldehyde reacts with ammonium acetate alone in ethanol at 0-5°C to produce the title compound, 2-(*o*-hydroxyphenyl)-5, 6-benzo-1, 3-oxazine (**4**). The formation of **4** was observed during an investigation of the products of hydrolysis of the benzopyran derivative **1** and in the course of the synthesis of substituted benzopyrans from aryl methyl ketones and cyclic ketones. Spectral data of **4** (UV, PMR, IR and mass) were compatible with its structure.

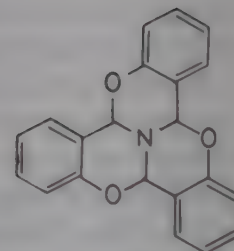
### 2-(*o*-Hydroxyphenyl)-5, 6-benzo-1, 3-oxazine (**4**)

Ammonium acetate (15.5 g, 0.20 mmol) was dissolved in ethanol (60 ml) by warming. The solution was cooled (20°C), and to this was added salicylaldehyde (20.9 ml, 0.20 mol) and the mixture kept at 0°C overnight (15 hr). The bright yellow crystals of **4** which separated out were filtered, washed with ethanol and dried, yield 10-11 g (22-25%), m.p. 164-66°C (depending upon the extent of dryness and the number of recrystallizations, the m.p. varied from 152° to 166°C); after four recrystallizations and drying **4** melted at 165 ± 1°C. The mother liquor contained more of **4** as found by TLC experiments; UV (EtOH): 254 ( $\epsilon$  = 5,800), 324 (1,900); PMR (DMSO):  $\delta$  8.71 (s, 1H,

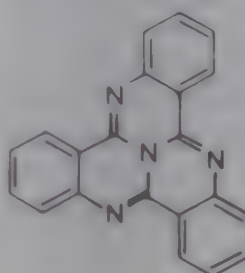


R, R' = H, alkyl, (CH<sub>2</sub>)<sub>3</sub>

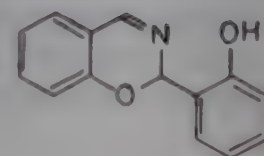
**1**



**2**



**3**



**4**

(OH), 7.5-6.55 (m, 9H, aromatic H and CH=N), 6.43 [s, 1H, O-CH(Ar)-N]; IR (KBr): 3400-3100 ( $\nu$  OH), 1620 ( $\nu$  C=N), 1600 (sh) and 1585 (sh) (aromatic  $\nu$  C=C), 1495 and 1455 (aromatic  $\nu$  C-H), 1400, 1280, 1220, 1063 ( $\nu$  C-O), 900, 850, 800 and 755 cm<sup>-1</sup> (out-of-plane aromatic C-H bending); MS (70 eV):  $m/z$  225 (M<sup>+</sup>, 100%), 226 (M+1, 16.2%), 224 (12.9), 197 (10.1), 196 (23.1), 132 (8), 122 (7), 121 (73), 120 (23), 107 (22.5), 106 (16.3), 105 (28.4), 102 (9.0), 93 (18), 78 (30), 77 (25), 66 (28), 65 (15), 51 (20).

### Acknowledgement

The authors thank Prof A R Venkitaraman for support and encouragement and the R and D Committee of the American College, Madurai, for partial financial support.

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## Efficient Conversion of Oxazoline-2-thione to Its 2-Oxo Derivative

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4, 5-Diphenyl-3-*p*-tolyl-4-oxazoline-2-thione (**1**) has been converted 2-oxo analogue (**2**) using (i) methyl iodide and methanol, (ii) sodium nitrite and dil. HCl and (iii) mercuric oxide, acetic anhydride and water.

Conversion of cyclic carbonyl compounds to their corresponding thio analogues using tetraphosphorus decasulphide<sup>1</sup> or Lawesson reagent<sup>2</sup> has been reported. Our interest in the synthesis of trisubstituted 4-oxazolin-2-ones and 2-thiones<sup>3</sup> prompted us to explore some methods for the reverse process. The present note describes three efficient and convenient approaches for the conversion of a triaryl-4-oxazoline-2-thione into the corresponding 2-one derivative in good yields.

The reaction of 4, 5-diphenyl-3-*p*-tolyl-4-oxazoline-2-thione (**1**) with methyl iodide in aq. methanol at reflux temperature gave a white solid which was characterised as 4, 5-diphenyl-3-*p*-tolyl-4-oxazoline-

2-one (**2**) by direct comparison (m.m.p., co-IR) with an authentic sample<sup>3</sup>. This method seems to operate through a 2-methylmercapto iodide intermediate (**a**) which on hydrolysis affords **2** (Scheme 1). Methyl iodide has been used earlier for conversion of thiones to methyl mercaptoiodides<sup>4</sup>.

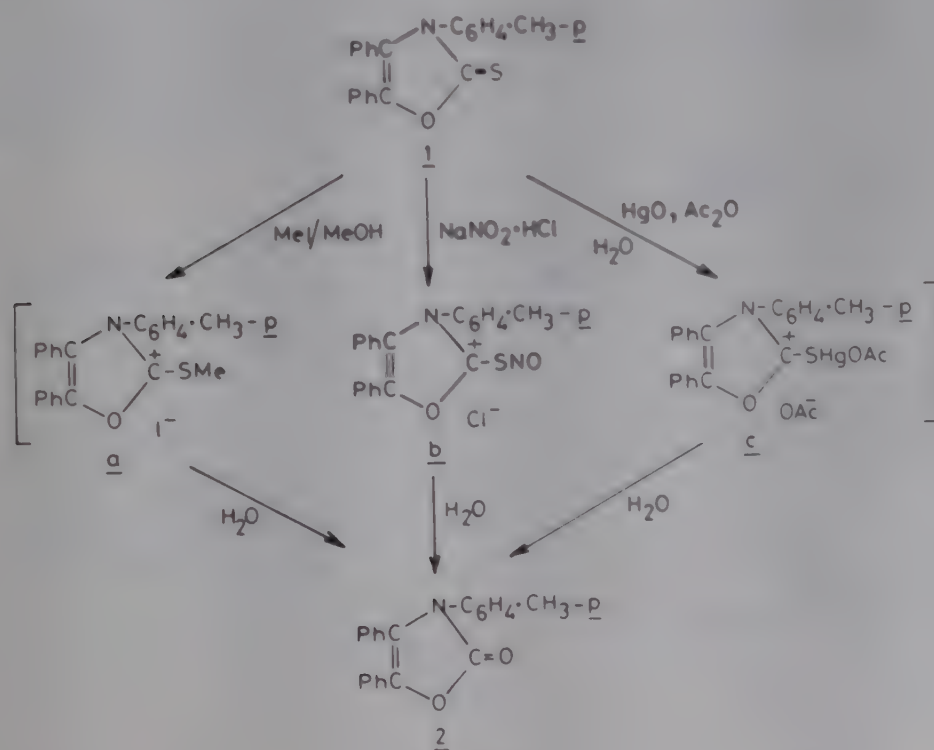
In the second approach, **1** on reaction with sodium nitrite and HCl led to **2** via a nitroso intermediate (**b**) formed by the attack of soft acid NO<sup>+</sup> on soft sulphur in **1** (see ref. 5) which on hydrolysis afforded the desired **2** and elemental sulphur<sup>6</sup> (Scheme 1). Electrophilic nitrosation of thiourea by nitrous acid at low pH has been reported earlier<sup>7</sup>.

In the third approach, the above conversion was effected using mercuric oxide, acetic anhydride and water. The attack of C=S in **1** on mercuric acetate leads to a cationic intermediate (**c**) which on hydrolysis gives **2** (Scheme 1). Earlier, isothioniones have been converted into isodithiones by reaction with mercuric oxide, acetic anhydride and water<sup>8</sup>.

4, 5-Diphenyl-3-*p*-tolyl-4-oxazoline-2-thione (**1**) and the authentic **2** were prepared according to the methods described earlier<sup>3</sup>.

### Method (i)

A mixture containing **1** (100 mg), methyl iodide (1 ml) and redistilled methanol (20 ml) was heated to



Scheme 1

reflux for 2 hr. The solvent was evaporated under reduced pressure and the residual matter crystallized from ethanol to give **2** yield 58% (55 mg).

#### Method (ii)

An aq. solution containing excess of  $\text{NaNO}_2$  (10 ml) was added dropwise to a mixture containing **1** (200 mg), dil.  $\text{HCl}$  (10%, 25 ml) and  $\text{CH}_2\text{Cl}_2$  (30 ml), stirred for 45 min at room temperature and extracted with  $\text{CH}_2\text{Cl}_2$  (50 ml). The organic layer was washed with water and dried ( $\text{MgSO}_4$ ). Evaporation of the solvent under reduced pressure followed by crystallisation of the residue from ethanol afforded **2** in 80% yield (152 mg).

#### Method (iii)

A mixture containing **1** (100 mg), yellow  $\text{HgO}$  (250 mg), acetic anhydride (10 ml) and water (20 ml) was heated to reflux for 45 min. The solid material

separated was filtered, washed with water and crystallized from ethanol to give **2** in 78% yield (74 mg).

We are thankful to the CSIR, New Delhi for the award of poolship to one of us (JR).

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## *meta*-Chloroperbenzoic Acid Oxidation of Fatty Azirines: Synthesis of Fatty Vicinal Nitroso-oxo Compounds

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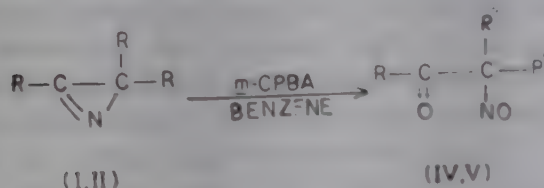
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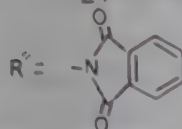
*m*-Chloroperbenzoic acid oxidation of fatty 2-phthalimido-2*H*-azirines(I,II and III) results in the formation of respective nitroso-oxo derivatives (IV,V and VI). In the case of azirine III, oximino-oxo derivative (VII) is also formed. The products have been characterized on the basis of spectral data.

Several papers have been published from the authors' laboratory<sup>1-5</sup> exploiting the reagent nitrosylchloride (NOCl) for the synthesis of fatty nitrosochloro derivatives. We report here for the first time a new route for the formation of vicinal nitroso-oxo compounds in quantitative yield by the oxidation of fatty azirines with *m*-chloroperbenzoic acid (*m*-CPBA).

2(3)-(7-Carbomethoxyheptyl)-3(2)-methyl-2-phthalimido 2*H*-azirine (I) on oxidation with a two-fold excess of *m*-CPBA at room temperature afforded a blue liquid which was characterized as methyl 9(10)-nitroso-10(9)-oxo-9(10)-phthalimidoundecanoate (IV; Scheme 1) on the basis of spectral data. The product IV showed a characteristic IR band at 1570 cm<sup>-1</sup> for nitroso group. A broad band appeared at 1740-1690 cm<sup>-1</sup> for carbonyl functions of keto, ester and phthalimido groups. The bands at 1610 and 710 cm<sup>-1</sup> accounted for the presence of disubstituted benzene ring.



I, IV : R = CH<sub>3</sub>; R' = (CH<sub>2</sub>)<sub>7</sub>COOCH<sub>3</sub> and  
R = (CH<sub>2</sub>)<sub>7</sub>COOCH<sub>3</sub>; R' = CH<sub>3</sub>  
II, V : R = CH<sub>3</sub>(CH<sub>2</sub>)<sub>7</sub>; R' = (CH<sub>2</sub>)<sub>7</sub>COOCH<sub>3</sub> and  
R = (CH<sub>2</sub>)<sub>7</sub>COOCH<sub>3</sub>; R' = CH<sub>3</sub>(CH<sub>2</sub>)<sub>7</sub>

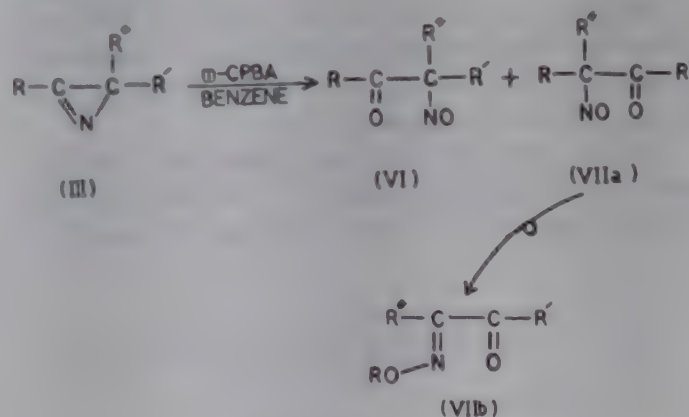


SCHEME 1

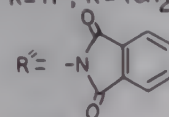
The PMR signals at  $\delta$ 1.75 [*s*, 3H, CH<sub>3</sub>-C(NO)-], 2.1 (*s*, 3H, CH<sub>3</sub>-CO-), 2.3 (*m*, 4H, -CH<sub>2</sub>-CO- and -CH<sub>2</sub>COOCH<sub>3</sub>) and 7.85 (*m*, 4H, Ar-H) alongwith other usual signals of fatty methyl ester clearly established the formation of isomeric product(IV). This isomeric nature was further confirmed by a study of its mass spectral fragmentation pattern. The molecular ion peak at *m/z* 388 was followed by the ion peaks at *m/z* 203, 185 and 173 (203 — NO), and 345, 315 (345 — NO), 199 (345 — C<sub>8</sub>H<sub>4</sub>O<sub>2</sub>N) and 43 (base peak).

A similar oxidation of 2(3)-(7-carbomethoxyheptyl)-3(2)-octyl-2-phthalimido-2*H*-azirine (II) with *m*-CPBA gave a blue liquid which was identified as isomeric methyl 9(10)-nitroso-10(9)-oxo-9(10)-phthalimidooctadecanoate (V) on the basis of its spectral data. The IR spectrum of V displayed a characteristic signal at 1570 cm<sup>-1</sup> for nitroso group. Its PMR displayed signals at  $\delta$ 2.28 (*m*, 4H, -CH<sub>2</sub>-CO- and C H<sub>2</sub>COOCH<sub>3</sub>) and 7.72(*m*, 4H, Ar-H) alongwith usual signals associated with fatty methyl ester. Its mass spectral fragmentation clearly indicated its isomeric nature. The molecular ion peak at *m/z* 486 was followed by the ion fragments at *m/z* 141, 345, 347, (345+2H), 199 (345 — C<sub>8</sub>H<sub>4</sub>O<sub>2</sub>N) and 315 (345 — NO), and 185, 301, 303 (301+2H) and 271 (301 — NO) which also furnished the information about the isomeric nature of V.

Similarly, *m*-CPBA oxidation of 2(3) (8-carbomethoxyoctyl)-2-phthalimido-2*H*-azirine(III) yields two products VI and VIIb (Scheme 2). The product VI,



III : R = H ; R' = (CH<sub>2</sub>)<sub>8</sub>COOCH<sub>3</sub> and  
R = (CH<sub>2</sub>)<sub>8</sub>COOCH<sub>3</sub>; R' = H  
VI, VIIa, VIIb : R = H ; R' = (CH<sub>2</sub>)<sub>8</sub>COOCH<sub>3</sub>



SCHEME 2

obtained as a blue liquid, in its IR spectrum showed a characteristic band for nitroso group at  $1575\text{ cm}^{-1}$ .

O

Appearance of PMR signals at  $\delta$  8.1 (s, 1H, O=CH), 2.78 (m, 2H,  $-\text{CH}_2-\text{COOCH}_3$ ) alongwith usual signals of fatty methyl ester established the structure of VI as methyl 10-nitroso-11-oxo-10-phthalimidoundecanoate. The mass ion peaks at  $m/z$  388 ( $\text{M}^+$ ), 359 ( $\text{M}-\text{CHO}$ ), 358 ( $\text{M}-\text{NO}$ ), 329 ( $\text{M}-\text{COOCH}_3$  or  $359-\text{NO}$ ), 300 ( $359-\text{COOCH}_3$ ), 217, 213 ( $359-\text{C}_8\text{H}_4\text{NO}_2$ ) and 104 (base peak,  $\text{C}_6\text{H}_4\text{CO}^+$ ) clearly supported the structure VI.

The product VIIb obtained as viscous liquid was characterized as methyl 11-oximino-10-oxo-11-phthalimidoundecanoate. Its IR spectrum exhibited diagnostic bands at  $3450 (=NOH)$  and  $1630\text{ cm}^{-1} (\text{C}=\text{N})$ . The PMR spectrum of VII displayed characteristic signals at  $\delta$  7.81 (m, 4H, Ar-H), 5.04 (s, 1H, =NOH,  $\text{D}_2\text{O}$  exchangeable) and 2.27 (m, 4H,  $-\text{CO}-\text{CH}_2-\text{CH}_2-\text{COOCH}_3$ ) alongwith usual signals. The mass spectrum gave the molecular ion peak at  $m/z$  388 which was followed by an ion peak at 371 ( $\text{M}-\text{OH}$ ). The ion peaks at  $m/z$  199, 189, 217, 232 (McLafferty ion) established the structure VIIb.

Formation of nitroso-oxo derivatives (IV, V and VI) from the *m*-CPBA oxidation of azirines (I, II and III) is shown in Scheme 3. The carbon-nitrogen double bond ( $\text{C}=\text{N}$ ) of azirine is epoxidised in the first step to give bicyclic aziridine (detected by low temperature IR, unstable intermediate) which on aerial or *m*-CPBA oxidation gave the nitroso-oxo derivatives.

The compound VI, isolated as a homogenous product, is expected to contain isomer VIIa since the reaction mixture of azirine III oxidation is likely to furnish an isomeric mixture but isomer VI predominates over VIIa because the latter isomer is supposed to rearrange to give the product VIIb, which was also isolated as a homogenous product.

The spectroscopic and chromatographic methods used have been given elsewhere<sup>3-5</sup>. The isomeric fatty azirines I (m.p.  $150^\circ$ ), II (m.p.  $132^\circ$ ) and III (m.p.  $55^\circ$ )

were prepared<sup>6</sup> by the oxidation of *N*-aminophthalimide with lead tetraacetate (LTA) in the presence of acetylenic fatty acid esters, methyl 9-undecynoate, methyl 9-octadecynoate and methyl 10-undecynoate, respectively.

#### Reaction of I with *m*-CPBA

Azirine I (1g, 2.8 mmol) was treated with *m*-CPBA (9.7g, 5.6 mmol) in benzene (50ml) in the dark at room temperature for 48 hr and the reaction mixture worked-up by extracting with aq. sodium carbonate (5%), drying the benzene layer over anhyd.  $\text{Na}_2\text{SO}_4$ , filtering, and evaporating the solvent in the dark when IV was obtained as a blue liquid in a quantitative yield; IR: 1740-1690, 1610, 1570 (NO), 1470, 1440, 1370, 1280, 1250, 1080, 880, 750 and  $710\text{ cm}^{-1}$ ; PMR ( $\text{CDCl}_3$ )  $\delta$  1.27 (brs, chain  $-\text{CH}_2-$ ), 1.75 [s, 3H,  $\text{CH}_3-\text{C}(\text{NO})-$ ], 2.3 (m, 4H,  $-\text{CO}-\text{CH}_2-$  and  $\text{CH}_2\text{COOCH}_3$ ), 2.1 (s, 3H,  $\text{CH}_3-\text{CO}$ ), 3.67 (s, 3H,  $-\text{COOCH}_3$ ), 7.85 (m, 4H, Ar-H); MS (70 eV):  $m/z$  388 ( $\text{M}^+$ , 1%), 345 (3), 315 (5), 203 (5), 199 (6), 185 (10), 173 (8), 43 (100).

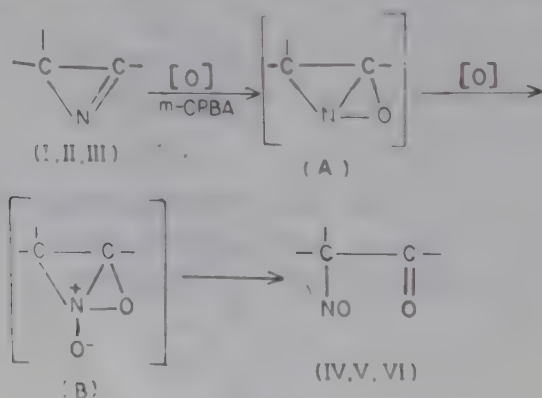
#### Reaction of II with *m*-CPBA

The azirine II (1g, 2.2 mmol) was treated with *m*-CPBA (7.6g, 4.4 mmol) in benzene (50 ml) as described above. After usual work-up, the product V was obtained as a blue liquid in a quantitative yield; IR: 1745-1690, 1610, 1570, 1520, 1460, 1430, 1370, 1280, 1250, 1140, 1070, 880, 750 and  $710\text{ cm}^{-1}$ ; PMR ( $\text{CDCl}_3$ ):  $\delta$  0.87 (t, 3H, terminal  $\text{CH}_3$ ), 1.27 (br s, chain  $-\text{CH}_2-$ ), 2.28 (m, 4H,  $-\text{CH}_2-\text{CO}-$  and  $-\text{CH}_2\text{COOCH}_3$ ), 3.66 (s, 3H,  $-\text{COOCH}_3$ ), 7.72 (m, 4H, Ar-H); MS (70 eV):  $m/z$  486 (1%), 347 (2), 345 (1), 315 (3), 303 (2), 301 (1), 271 (1), 199 (13), 185 (23), 141 (16) and 43 (100).

#### Reaction of III with *m*-CPBA

The azirine III (1g, 2.8 mmol) on similar treatment with *m*-CPBA (9.7g, 5.6 mmol) and work-up gave a viscous liquid which showed two components on TLC. The viscous liquid was chromatographed over a silica gel (20g) column. Elution with pet. ether-ether (75:25, v/v) gave VI as a blue liquid (65%); IR: 1690-1740, 1580, 1470, 1440, 1365, 1280, 1250, 1200, 1080, 880, 750 and  $710\text{ cm}^{-1}$ ; PMR ( $\text{CDCl}_3$ ):  $\delta$  1.3 (br s, chain  $-\text{CH}_2-$ ), 2.25 (br m, 2H,  $\text{CH}_2\text{COOCH}_3$ ), 3.66 (s, 3H,  $-\text{COOCH}_3$ ), 7.8 (m, 4H, Ar-H) and 8.1 (s, 1H, O=C-H); MS (70 eV):  $m/z$  388 (1%), 359 (4), 358 (2), 329 (2), 300 (3), 217 (6), 213 (2) and 104 (100).

Further elution with pet. ether-ether 70:30, v/v gave VIIb as a viscous liquid (31%); IR: 3450 (OH), 1740-1690, 1630, (C=N), 1480, 1440, 1360, 1210, 1080, 880, 750 and  $710\text{ cm}^{-1}$ ; PMR ( $\text{CDCl}_3$ ):  $\delta$  1.3 (br s, chain  $-\text{CH}_2-$ ), 2.28 (m, 4H,  $-\text{CO}-\text{CH}_2-$  and  $-\text{CH}_2\text{COOCH}_3$ ), 3.65 (s, 3H,  $-\text{COOCH}_3$ ), 5.04 (s, 1H, =N-OH,  $\text{D}_2\text{O}$  exchangeable) and 7.81 (m, 4H, Ar-



SCHEME 3

H); MS (70 eV):  $m/z$  388 (1%), 371 (5), 232 (16), 217 (9), 199 (7), 189 (13) and 104 (100).

We thank Prof. M S Ahmad, Chairman, Department of Chemistry, AMU, Aligarh for providing research facilities and the CSIR, New Delhi for the award of a research associateship to one of us (M H A).

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## Reactions of Aminopyridine Derivatives with 1-Aryl-3-phenyl-2-propyn-1-ones

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1-Aryl-3-phenyl-2-propyn-1-ones (Ia-c) react with 2-amino-(IIa)- and 2-amino-5-chloro-(IIb)-pyridines to give 3-(pyrid-2-ylamino)-(IIIa-c)- and 3-(5-chloropyrid-2-ylamino)-(IIId-f)-1-aryl-3-phenyl-2-propen-1-ones, respectively. 2, 3-Diamino-pyridine reacts with Ib and Ic to give 1-Aryl-3-phenyl-3-(2-amino-3-iminopyrid-3-yl)-2-propen-1-ones (Va-Vb) and pyrido [3, 2-b] [1, 4] diazepines (VIb, VIc). However, reaction of Ia with 2, 3-diaminopyridine gives only the diazepine (VIa). The structures of the products are based on elemental analyses and spectral data.

In our earlier studies<sup>1-3</sup> we have reported the reactions of 1-aryl-3-phenyl-2-propyn-1-ones with primary and secondary aromatic amines and phenylenediamines. In the present investigation the reactions of 1-aryl-3-phenyl-2-propyn-1-ones (Ia-c) with heterocyclic amin-

es such as 2-amino-, 2-amino-5-chloro' and 2, 3'diamino-pyridines have been studied with a view to establishing the structure and/or configuration of the products as well as scope of the reactions.

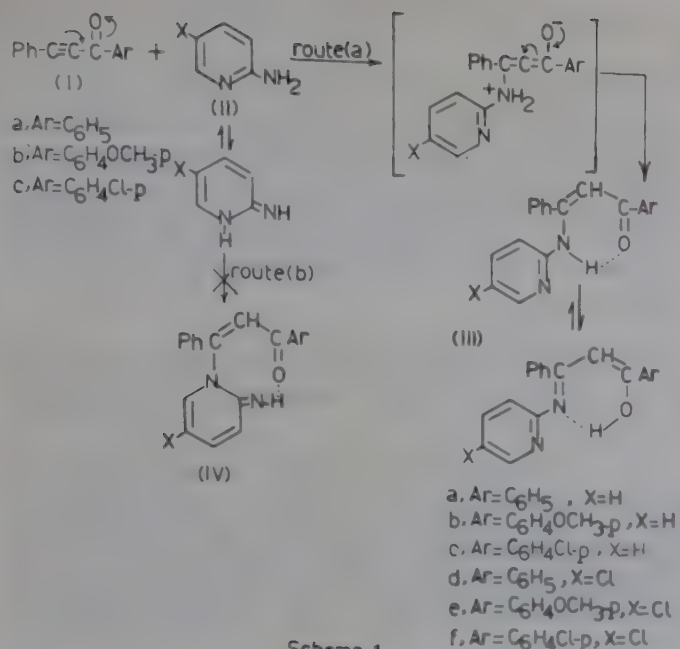
The reaction of 2-amino-(IIa)- and 2-amino-5-chloro-(IIb)-pyridines with I in equimolar amounts in ethanol under reflux for 5 hr gave 3-(pyrid-2-ylamino)-(IIIa-c)- and 3-(5-chloropyrid-2-ylamino)-(IIId-f)-1-aryl-3-phenyl-2-propen-1-ones (Table I), respectively (Scheme 1).

The structures of these products were established by elemental analyses and spectral data. Their IR spectra exhibited two stretching bands in the region 1610-1570 due to C=O and/or C=N- functions in addition to a strong broad band at 3460-3440 cm<sup>-1</sup> due to OH and/or NH group<sup>4</sup>. The electronic spectra of these compounds were identical indicating their structural analogy and displayed four absorption maxima at 368-380, 284-290, 252-260 and 226-230 nm. The PMR spectra of IIIa-f showed signals at  $\delta$ 6.14-6.20 (s, CH=), 8.13-6.25 (m, Ar-H) and 12.65-12.80 (br, OH). The

Table I-Crystallized Data of the Compounds III, V and VI

Compd	m.p. °C	Crystallized from *	Yield (%)	Mol. formula	Found (%) (Calc)		
					C	H	N
IIIa <sup>6</sup>	113-14	M	80	C <sub>20</sub> H <sub>16</sub> N <sub>2</sub> O	80.4 (80.2)	5.2 5.1	9.4 (9.4)
IIIb	126-27	P <sub>c</sub> +B	74	C <sub>21</sub> H <sub>18</sub> N <sub>2</sub> O <sub>2</sub>	76.6 (76.3)	5.7 5.5	8.7 (8.5)
IIIc	130-31	M	85	C <sub>20</sub> H <sub>14</sub> ClN <sub>2</sub> O	71.5 (71.7)	5.0 4.5	8.5 (8.4)
IIId	122-23	P <sub>b</sub>	63	C <sub>20</sub> H <sub>14</sub> ClN <sub>2</sub> O	71.7 (71.7)	5.1 4.5	8.5 (8.4)
IIIe	127-28	P <sub>b</sub>	60	C <sub>21</sub> H <sub>17</sub> ClN <sub>2</sub> O	69.3 (69.1)	4.7 4.7	7.8 (7.7)
IIIf	133-34	P <sub>c</sub>	44	C <sub>20</sub> H <sub>14</sub> Cl <sub>2</sub> N <sub>2</sub> O	64.6 (65.1)	4.5 4.0	7.7 (7.6)
Va	198-99	P <sub>c</sub> +B	58	C <sub>21</sub> H <sub>16</sub> N <sub>3</sub> O <sub>2</sub>	72.9 (73.0)	5.7 5.5	12.3 (12.2)
Vb	196-97	P <sub>c</sub> +B	50	C <sub>20</sub> H <sub>16</sub> ClN <sub>3</sub> O	69.0 (68.7)	4.3 4.6	12.3 (12.0)
VIa	300-301	T+E	52	C <sub>35</sub> H <sub>25</sub> N <sub>3</sub> O	83.3 (83.5)	5.3 5.0	8.5 (8.3)
VIb	296-97	B+P <sub>c</sub>	32	C <sub>37</sub> H <sub>29</sub> N <sub>3</sub> O <sub>3</sub>	78.9 (78.8)	5.4 5.2	8.0 (7.5)
VIc	306-307	B	33	C <sub>35</sub> H <sub>23</sub> Cl <sub>2</sub> N <sub>3</sub> O	73.6 (73.4)	5.2 5.1	7.7 (7.3)

\*M=Methanol, P<sub>c</sub>=light petrol (40-60°), P<sub>b</sub>=light petrol (60-80°), P<sub>c</sub>=light petrol (80-100°), B=benzene, T=toluene and E=ethanol.



Scheme 1

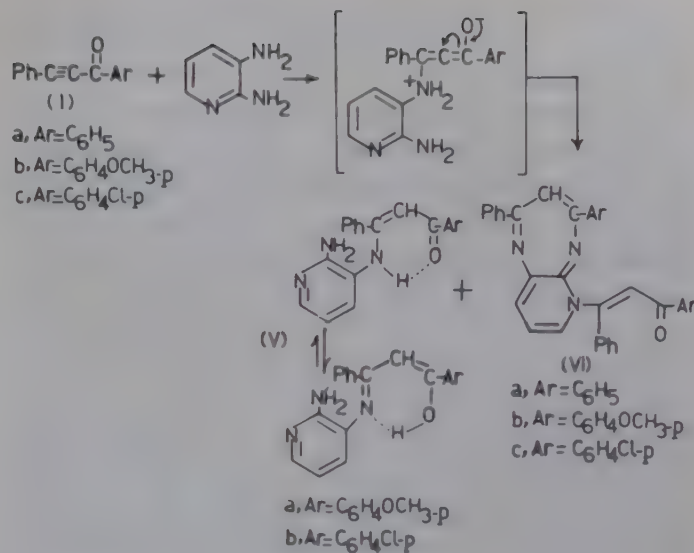
PMR spectra of IIIb and IIIe displayed an additional signal at  $\delta 3.83$  due to  $-\text{OMe}$  protons.

It appears that the reaction takes place through the nucleophilic attack of *exo*- rather than *endo*-nitrogen of 2-aminopyridine (nucleophile) on the  $\beta$ -acetylenic carbon of I. This is evident by deshielding of the acidic proton in the PMR spectra of the products, and is consistent with a proton attached to an oxygen atom rather than to a nitrogen atom. Hence, structure IV was excluded. The mass spectra of the products further supported the assigned structure III.

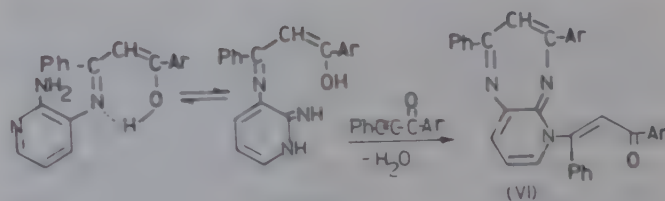
Treatment of Ib and Ic with an equimolar amount of 2,3-diaminopyridine gave the 1:1 adducts, 1-aryl-3-phenyl-3-(2'-amino-3'-iminopyrid-3'-yl)-2-propen-1-ones (Va and Vb) together with a small amount of pyrido [3,2-*b*] [1,4] diazepines (VIb and VIc). However, treatment of Ia with 2,3-diaminopyridine gave only the diazepine VIa (cf. Scheme 2)

The structure of Va and Vb were confirmed by elemental analyses and spectral data. Their IR spectra exhibited stretching bands due to  $\text{C}=\text{O}$  and/or  $\text{C}=\text{N}$  functions in the region 1635-1605 in addition to three absorption bands in the region 3450-3160  $\text{cm}^{-1}$  attributable to the symmetrical and asymmetrical stretching vibrations of the vibrationally coupled NH bonds of a primary amino function and the absorption due to 3-NH group. Their electronic spectra reflected their structural analogy and displayed five absorption maxima at 372-374, 330-340, 288-290, 260 and 224-232 nm. The PMR spectra of V exhibited two broad singlets at  $\delta 4.87$  (2H,  $\text{NH}_2$ ) and 12.5 (1H, OH) which disappeared on shaking with  $\text{D}_2\text{O}$ . Their mass spectra displayed a peak at  $m/z$  210 which probably resulted from the loss of  $p\text{-CH}_3\text{OC}_6\text{H}_4\text{CO-}$  from Va or  $p\text{-ClC}_6\text{H}_4\text{CO-}$  from Vb.

The structural assignments of the diazepines (VIa-c)



Scheme 2



Scheme 3

were based on elemental analyses and spectral data. Their IR and PMR spectra indicated the absence of NH and/or OH functions. The PMR spectra of VIa-c exhibited multiplets at  $\delta 8.4$ -6.6 due to aromatic and vinyl protons which could not be resolved and two different signals for the two  $-\text{OMe}$  groups at  $\delta 3.88$  and 3.75 in case of VIb.

It seems that the formation of the diazepines (VIa-c) involves the reaction of one molecule of 2,3-diaminopyridine and two molecules of I with subsequent elimination of one molecule of water as shown in Scheme 3. All the spectral data are included in Table I.

Melting points are uncorrected. Electronic and IR spectra were recorded on a Pye-Unicam SP 8-500 UV-vis and a Pye-Unicam SP 1025 spectrophotometers, respectively, PMR spectra on a Jeol FX 90 Q spectrophotometer and mass spectra on a Kratos MS 30 mass spectrometer at 70 eV. The spectral data of only the representative compounds have been given.

The required 1-aryl-3-phenyl-2-propyn-1-ones (Ia-c) were prepared according to the method described by Barker and coworkers<sup>5</sup>.

1-Aryl-3-phenyl-3-(pyrid-2-ylamino)- and 1-aryl-3-phenyl-3-(5-chloropyrid-2-ylamino)-2-propen-1-ones (IIIa-f; Table I):

#### General procedure

A solution of 2-amino-(IIa)- or 2-amino-5-chloro-

(IIb)-pyridine (0.005 mol) in ethanol (10 ml) was added to a solution of I (0.005 mol) in ethanol (20 ml) and the reaction mixture refluxed on a water-bath for 48 hr, solvent removed under reduced pressure and the brownish red oil, thus obtained, chromatographed on activated alumina column in benzene using ether-light petrol (b.p 40-60°) (1:1; v/v) as eluant to give a solid product. Recrystallisation from a suitable solvent gave 1-aryl-3-phenyl-3-(pyrid-2-ylamino)-(IIIa-c)- or 1-aryl-3-phenyl-3-(5-chloro-2-ylamino)-(IIId-f)-2-propen-1-ones, (cf. Table 1). IIIb-IR (nujol): 3460 br(OH), 1605 m and 1580 s(C=O and/or C=N)  $\text{cm}^{-1}$ , UV (EtOH): 368 (log  $\epsilon$  4.39), 290 (3.91), 252 (4.10) and 228 nm (4.03); PMR ( $\text{CDCl}_3$ ):  $\delta$  6.2 (s, 1H, CH=), 6.3-8.4 (m, 14H, Ar-H) and 12.8 (br, 1H, OH); MS:  $m/z$  330 ( $\text{M}^+$ ; 0.6%), 195 (M-PhCO; 100%) and 105 (PhCO; 8%).

*Addition of 2, 3-diaminopyridine to 1-aryl-3-phenyl-2-propyn-1-ones (Ia-c): Formation of 3-(2-amino-3-iminopyrid-3-yl)-1-aryl-3-phenyl-2-propen-1-ones (V) and pyrido [3, 2-b] [1, 4] diazepines (VI) (Table 1)*

To a solution of I (0.001 mol) in ethanol (20 ml) was added a solution of 2, 3-diaminopyridine (0.001 mol) in ethanol (10 ml) and the reaction worked-up as described above. The dark brown oil, obtained after evaporation of the solvent, was treated with dil. methanol and left at room temperature for several days to give a solid product. The precipitated solid was

fractionally crystallised from a suitable solvent to give V.

Va-IR (nujol): 3450 w, 3300 w, 3160 br (OH), 1635 m and 1600 (C=O and/or C=N)  $\text{cm}^{-1}$ ; UV (EtOH): 372 (log  $\epsilon$  4.46), 330 (4.30), 290 (4.23), 260 (4.10), 224 nm (4.37); PMR ( $\text{CDCl}_3$ ):  $\delta$  3.86 (s, 3H,  $\text{OCH}_3$ ), 4.89 (br, 2H,  $\text{NH}_2$ ), 6.17 (s, 1H, CH=), 6.27-8.04 (m, 12H, ArH), 12.42 (br, 1H, OH); MS:  $m/z$  345 ( $\text{M}^+$ ; 41%), 210 (M-COC<sub>6</sub>H<sub>4</sub>OCH<sub>3</sub>-p).

The insoluble solid remained after separation of V was recrystallised from an appropriate solvent to give VI.

VIa-IR (nujol): 3450 w, 3290 w, 3140 br(OH), 1635 m, 1605 sh(C=O and/or C=N)  $\text{cm}^{-1}$ ; UV (EtOH): 374 (log  $\epsilon$  4.11), 340 (3.98), 288 (3.85), 260 (4.00), 232 nm (3.99); PMR ( $\text{CDCl}_3$ ):  $\delta$  4.87 (br, 2H,  $\text{NH}_2$ ), 6.14 (s, 1H, CH=), 6.29-7.95 (m, 12H, ArH), 12.50 (br, 1H, OH).

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## A New Route for the Synthesis of 2-Amino-biphenyls Involving Enamine Rearrangement of Pyridinium Salts†

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2-Benzyl-1-methylpyridinium iodides (IIa-c) undergo ring opening and recyclization reactions when heated with aq. sodium hydroxide to give 2-methylaminobiphenyls (IIIa-c). The effect of aq. alkylamine and alkylammonium sulphite solution on this type of reaction has also been studied.

Fadda and coworkers<sup>1-6</sup> have reported that recyclization of 1-alkylpyridinium salts in the presence of aq. alkali, alkylamine or alkylammonium sulphite gives the aminobiphenyl derivatives. The nature and position of substituent in the pyridine ring have a considerable effect on this type of reaction<sup>7</sup>. Thus, it was expected that 2-benzylpyridinium salts having an alkyl radical in different positions in the pyridine ring would undergo recyclization reaction.

In the present study, the action of aq. ethanolic sodium hydroxide on 2-benzyl-1-methylpyridinium iodides (IIa-c) led to the formation of 2-methylaminobiphenyls (IIIa-c) in 10-15% yield.

Similarly, in the presence of methylamine the yield of IIIa-c increased to 20%, besides the formation of 2-hydroxybiphenyls (IVa-c) (8%) and 2-benzylpyridine derivatives (Ia-c) (45%).

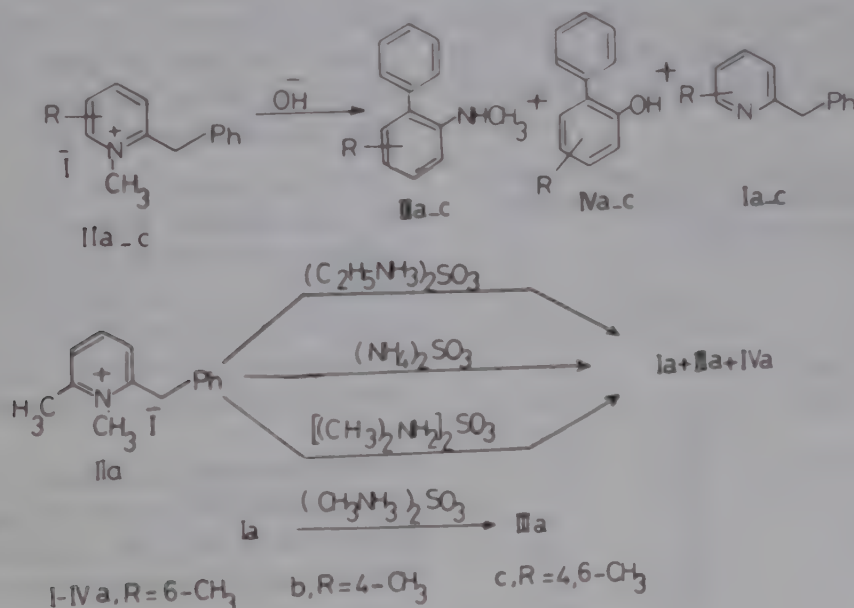
On the other hand, 2-benzyl-1, 6-dimethylpyridinium iodide (IIa) when heated with methylammonium sulphite afforded 6-methyl-2-methylaminobiphenyl (IIIa) (60%). Similarly, 2-ethylamino-6-methylbiphenyl (IIIId) (53%) was obtained on heating 2-benzyl-1-ethyl-6-methylpyridinium iodide (IIId) with ethylammonium sulphite. At the same time 2-benzyl-6-methylpyridine (I) was obtained as an N-dealkylation product in 10% yield. However, IIb and IIc failed to give the corresponding aminobiphenyls probably due to steric hinderance offered by the methyl groups in positions 4 and 6 and instead the parent 2-benzylpyridine derivatives (Ib, c) were obtained by direct attack of the nucleophile on the CH<sub>3</sub>-N bond.

Analogous to the reaction reported earlier<sup>6</sup>, the action of methylammonium sulphite on IIId afforded 6-methyl-2-methylaminobiphenyl (IIIa) (61%), 2-hydroxy-6-methylbiphenyl (IVa) (10%) and 2-benzyl-6-methylpyridine (Ia) (12%).

On the other hand, treatment of ethylammonium sulphite with IIa afforded IIIa as the main product (36%) along with the IVa (10%). However, the action of dimethylammonium sulphite on IIa produced IIIa (6%), IVa (20%) and Ia (50%).

On using aq. ammonia we found that recyclization reaction occurred without exchange of the methyl-amino fragment by amino and the reaction products were found to be IIIa (5%), IVa (15%) and Ia (60%).

The action of methylammonium sulphite on the unquaternized 2-benzyl-6-methyl pyridine (Ia) was also studied. The products in this case were found to be



†Part VII of the series, Enamine Rearrangement of Pyridinium Salts.

IIIa (30%) and IVa (13%). However, when zinc chloride was used as a catalyst<sup>5</sup>, the yield of IIIa increased to 53%.

#### Substituted 2-benzylpyridines (Ia-c)

The following compounds were prepared according to the literature procedure<sup>8</sup>:

**2-Benzyl-6-methylpyridine (Ia):** Yield (19%), b.p. 150-153°/14 mm (lit.<sup>8</sup> 150°/13 mm);  $R_f$  0.69; PMR (CCl<sub>4</sub>);  $\delta$  2.3 (s, 3H, CH<sub>3</sub>), 4.0 (s, 2H, CH<sub>2</sub>), 6.7-7.7 (m, 8H, Ar-H); UV (EtOH): 250 nm (log  $\epsilon$  4.21); MS:  $m/z$  183 (M<sup>+</sup>; 100%).

**2-Benzyl-4-methylpyridine (Ib):** Yield (35%), b.p. 106°/0.6 mm;  $R_f$  0.62; PMR (CCl<sub>4</sub>);  $\delta$  2.5 (s, 3H, CH<sub>3</sub>), 4.0 (s, 2H, CH<sub>2</sub>), 6.7-7.8 (m, 8H, Ar-H); MS:  $m/z$  183 (M<sup>+</sup>; 100%).

**2-Benzyl-4, 6-dimethylpyridine (Ic):** Yield 30%; b.p. 157-160°/8 mm (lit.<sup>8</sup> 160°/6 mm);  $R_f$  0.69 NMR (CCl<sub>4</sub>);  $\delta$  2.2 (s, 3H, CH<sub>3</sub>), 2.5 (s, 3H, CH<sub>3</sub>), 4.0 (s, 2H, CH<sub>2</sub>) 6.6-7.8 (m, 7H, Ar-H); MS:  $m/z$  197 (M<sup>+</sup>; 100%).

#### Preparation of pyridinium salts (IIa-c): General procedure

A mixture of substituted 2-benzylpyridine (Ia-c) (0.02 mol) and methyl iodide (5.5g, 0.03 mol) was allowed to stand at room temperature for one day. The resultant yellow crystals were recrystallized from ethanol-ether (3:1) to give IIa-c (Table I).

#### 1-Ethyl-2-benzyl-6-methylpyridine (IIId)

A solution of 2-benzyl-6-methylpyridine (0.02 mol) and ethyl iodide (0.03 mol) was heated in a sealed tube at 150° for 2 hr. The product was crystallized as yellow crystals from ethanol-ether (3:1).

#### Recyclization of pyridinium salts (IIa-c) to the corresponding 2-methylaminobiphenyls (IIIa-c)

(A) To the compound II (0.01 mol) were added 20% NaOH solution (10 ml) and ethanol (1 ml), and the reaction mixture was heated for 2 hr under nitrogen atmosphere, cooled and extracted with ether. The ethereal extract was dried (MgSO<sub>4</sub>) and chromatog-

raphed over silica gel (100/160). Removal of solvent from benzene eluate under reduced pressure gave III. **6-Methyl-2-methylaminobiphenyl (IIIa):** Yield 13%, oil,  $R_f$  0.71; IR: 3420 cm<sup>-1</sup> (NH); PMR (CCl<sub>4</sub>);  $\delta$  2.3 (s, 3H, CH<sub>3</sub>), 2.8 (s, 3H, N-CH<sub>3</sub>), 3.9 (s, 1H, NH), 6.5-7.6 (m, 8H, Ar-H); MS:  $m/z$  197 (M<sup>+</sup>; 100%).

**4-Methyl-2-methylaminobiphenyl IIIb:** Yield 12%,  $R_f$  0.68; IR: 3420 cm<sup>-1</sup>; PMR (CCl<sub>4</sub>);  $\delta$  2.5 (s, 3H, CH<sub>3</sub>), 2.7 (s, 3H, N-CH<sub>3</sub>), 3.8 (s, 1H, NH), 6.6-7.6 (m, 8H, Ar-H); MS:  $m/z$  197 (M<sup>+</sup>; 100%).

**4,6-Dimethyl-2-methylaminobiphenyl (IIIc):** Yield (10%),  $R_f$  0.58; IR: 3420 cm<sup>-1</sup>; PMR (CCl<sub>4</sub>);  $\delta$  2.2 (s, 3H, CH<sub>3</sub>), 2.4 (s, 3H, CH<sub>3</sub>), 2.8 (s, 3H, N-CH<sub>3</sub>), 4.1 (s, 1H, NH), 6.7-7.8 (m, 7H, Ar-H); MS:  $m/z$  211 (M<sup>+</sup>; 100%).

(B) Aq. methylamine (20 ml, 35%) was added to II (0.2 mol), and the mixture heated in a sealed tube at 180° for 20-65 hr. The product was extracted with ether, dried (MgSO<sub>4</sub>) and chromatographed over silica gel (100/160). Elution with benzene gave the compounds III, IV and I.

**2-Hydroxy-6-methylbiphenyl (IVa):** Yield 8%,  $R_f$  0.56; PMR (CCl<sub>4</sub>);  $\delta$  2.3 (s, 3H, CH<sub>3</sub>), 6.1 (s, 1H, OH), 7.8-8.6 (m, 8H, Ar-H); MS:  $m/z$  184 (M<sup>+</sup>; 100%).

**2-Hydroxy-4-methylbiphenyl (IVb):** Yield 8%,  $R_f$  0.54; PMR (CCl<sub>4</sub>);  $\delta$  2.6 (s, 3H, CH<sub>3</sub>), 6.0 (s, 1H, OH), 7.4-8.5 (m, 8H, Ar-H); MS:  $m/z$  184 (M<sup>+</sup>; 100%).

**2-Hydroxy-4, 6-dimethylbiphenyl (IVc):** Yield 6%,  $R_f$  0.51; PMR (CCl<sub>4</sub>);  $\delta$  2.3 (s, 3H, CH<sub>3</sub>), 2.5 (s, 3H, CH<sub>3</sub>), 6.0 (s, 1H, OH), 7.5-8.6 (m, 7H, Ar-H); MS:  $m/z$  198 (M<sup>+</sup>; 100%).

#### Reaction of II with methylammonium sulphite: General Procedure

Aq. methylammonium sulphite (30 ml.) was added to II (0.02 mol) and the reaction mixture heated in a sealed tube at 180° for 30-35 hr. The product was extracted with ether, dried (MgSO<sub>4</sub>) and chromatographed over silica gel (100/160) using benzene as eluant. The eluate was dried and solvent removed under reduced pressure to IIIa or IIId.

IIIa was obtained from IIa in 74% yield,  $R_f$  0.71. IIId was obtained from IId and ethylammonium sulphite in 56% Yield,  $R_f$  0.68; IR: 3420 cm<sup>-1</sup> (NH); PMR (CCl<sub>4</sub>);  $\delta$  1.5 (s, 3H, CH<sub>3</sub>), 1.9 (t, 3H, N-CH<sub>2</sub>-CH<sub>3</sub>), 3.2 (q, 2H, N-CH<sub>2</sub>-CH<sub>3</sub>), 4.0 (s, 1H, NH), 6.3-7.6 (m, 8H, Ar-H); MS:  $m/z$  211 (M<sup>+</sup>; 100%).

#### 2-Benzyl-4-methyl- and 2-benzyl-4,6-dimethylpyridines (Ib,c)

Methylammonium sulphite was heated with IIb or IIc for 65 hr at 180° to give the N-dealkylation product (Ib or Ic) in 50-58% yield;  $R_f$  0.62 and 0.69 respectively.

#### Ring opening and reamination of the pyridinium salts

(A) Aq. methylammonium sulphite (30, 35%) was added to IIId (0.02 mol) and the reaction mixture

Table 1—Characterization Data of 1-Alkyl-2-benzylpyridinium Iodides (IIa-d)

Compd.	Yield (%)	m.p. °C	Mol. formula	Found(%)		(Calc.)
				C	H	
IIa	86	196	C <sub>14</sub> H <sub>16</sub> N	51.3 (51.7)	4.9 (4.9)	
IIb	90	205	C <sub>14</sub> H <sub>16</sub> N	52.0 (51.7)	4.7 (4.9)	
IIc	85	225	C <sub>15</sub> H <sub>18</sub> N	53.3 (53.1)	5.0 (5.3)	
IIId	87	218	C <sub>15</sub> H <sub>18</sub> N	53.5 (53.1)	5.2 (5.3)	

heated in a sealed tube at 150° for 30 hr and worked-up to give compound IIIa, IVa and Ia.

(B) Aq. ethylammonium and/or dimethylammonium sulphite (30 ml, 35%) was heated with IIa (0.02 mol) in a sealed tube at 150° for 40 hr and the reaction mixture worked-up to give IIIa, IVa and Ia.

(C) While using ammonium sulphite as recycling agent, the reaction mixture was heated in a sealed tube at 180° for 60-65 hr, and the product mixture worked-up to give IIIa, (5%), IVa, (15%) and Ia (58-60%).

#### *Recyclization of unquaternized pyridine base*

(A) To 2-benzylpyridine (Ia, 0.01 mol) was added methylammonium sulphite (20 ml) and the reaction mixture heated in a sealed tube at 180° for 60 hr. The resultant product was extracted with ether, dried ( $\text{MgSO}_4$ ) and chromatographed over silica gel (100/160) column using benzene-ethyl acetate (5:2) as eluant to give IIIa (30%), IVa (13%) and the unreacted Ia (57%).

(B) Reaction mixture consisting of aq. methylammonium sulphite (20 ml) and  $\text{ZnCl}_2$  (2.5g) was heated in a sealed tube at 180° for 60 hr. Analysis of the products showed the presence of IIIa (53%), IVa (18%) and Ia (29%).

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## A Simple Synthesis of Indeno [1,2-*b*]-quinolines

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A three-step synthesis of indeno [1,2*b*] quinolines (3) from indanone by treatment with POCl<sub>3</sub>/DMF followed by conversion of the resultant aldehyde (1) into anil hydrochlorides (2) and their thermal cyclization is described.

We have developed earlier a simple route for the synthesis of dihydrobenz[*c*] acridines<sup>1</sup>, some of which are found to be good fluorochromes for fixed smears<sup>2</sup>. This discovery inspired us to undertake the synthesis of dihydronaphthoquinolines and their ring homologs<sup>3</sup>. We report here the synthesis of the title compounds by an analogous method.

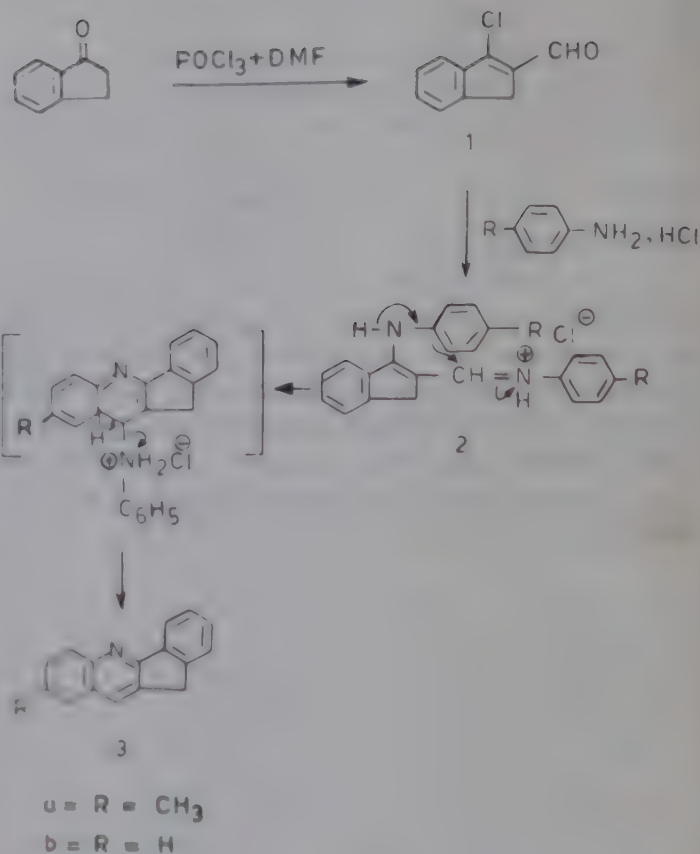
Indanone was treated with POCl<sub>3</sub> and DMF to get the chlorocarboxaldehyde (1) which on reaction with *p*-toluidine or aniline gave the anil (2) in nearly 80% yield. This anil derivative on brief heating at 250° readily underwent cyclization to a quinoline derivative<sup>4</sup> (3), the structure of which was established by spectral data and analogy with other systems<sup>5</sup>.

### 1-Chloro-3*H*-indene-2-carboxaldehyde (1)

Indanone (3.9 g, 0.03 mol) in DMF (5 ml) was added to a cooled (0°) and stirred solution of POCl<sub>3</sub> (6.4 g, 0.04 mol) in DMF (10 ml), and reaction mixture stirred for 2 hr at 0°. The resulting complex was poured into ice-water, allowed to stand overnight at 3° and organic material extracted with ether. The extract was washed with water, dried (Na<sub>2</sub>SO<sub>4</sub>) and solvent removed to furnish a semisolid mass which was passed through a short column of silica gel. Elution with pet. Ether (60-80°) gave 4.9 g (90%) of 1 as yellow crystals, m.p. 78-80°; IR (CHCl<sub>3</sub>): 2800 (C-H of CHO), 1650 (C=O, unsaturated) and 1620 cm<sup>-1</sup> (C=C); NMR (CDCl<sub>3</sub>): δ 4.7 (s, 2H, -CH<sub>2</sub>-), 7.5-7.8 (m, 4H, Ar-H) and 11.0 (s, 1H, CHO) (Found: C, 67.0; H, 3.7. C<sub>10</sub>H<sub>7</sub>OCl requires C, 67.2; H, 3.9%).

### 1-(*p*-Tolylamino)-2-(*p*-tolyliminomethyl)-3*H*-indene-hydrochloride (2a)

The chloroformyl derivative (1) (1.7 g) in ethanol (20 ml) was added to the cooled and stirred solution of *p*-toluidine (2.1 g) and 2*N* HCl (10 ml) in ethanol (50 ml). The reaction mixture was stirred for 2 hr and then



refluxed for 15 min. After cooling, the solid mass was filtered, washed with ethanol and dried to get 3.2 g (80%) of 2a m.p. 192° (Found: C, 77.0; H, 6.1. C<sub>24</sub>H<sub>23</sub>N<sub>2</sub>Cl requires C, 76.9; H, 6.2%).

### 1-Phenylamino-2-phenyliminomethyl-3*H*-indene hydrochloride (2b)

It was prepared from 1 (4 g in ethanol 47 ml) by the procedure as described for 2a, yield 5.6 g (80%), m.p. 160-62° (Found: C, 76.0; H, 5.3. C<sub>22</sub>H<sub>19</sub>N<sub>2</sub>Cl requires C, 76.2; H, 5.5%).

### 8-Methyl-11*H*-indeno [1,2-*b*] quinoline (3a)

The anil hydrochloride derivative 2a (1.5 g) was heated at 230° in a metal-bath for 5 min. The fused mass was dissolved in ether and washed with water. The organic layer was dried (Na<sub>2</sub>SO<sub>4</sub>), solvent removed and the residue crystallized from ether-pet. ether to get 3a, yield 0.5 g (40%), m.p. 124°; PMR (CDCl<sub>3</sub>): δ 2.5 (s, 3H, CH<sub>3</sub>), 4.0 (s, 2H, -CH<sub>2</sub>-), 7.5-7.8 (m, 8H, Ar-H); MS (70 eV): *m/z* 231 (M<sup>+</sup>; 100%) (Found: C, 88.5; H, 5.8. C<sub>17</sub>H<sub>13</sub>N requires C, 88.3; H, 5.7%).

### 11*H*-Indeno [1,2-*b*] quinoline (3b)

The anil derivative 2b (5 g) was heated at 170° for 5

min. Usual work-up of the reaction mixture gave **3b**, yield 1.7 g (49%), m.p. 130-32°; PMR (CDCl<sub>3</sub>) :  $\delta$  4.0 (s, 2H, -CH<sub>2</sub>-), 7.5-8.3 (m, 9H, Ar-H); MS (70 eV) :  $m/z$  217 (M<sup>+</sup>; 100%) (Found : C, 87.9; H, 4.9. C<sub>16</sub>H<sub>11</sub>N requires C, 88.2; H, 5.0%)

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## One-pot Synthesis of 2-Aryl-4-aroyl-9H-pyrido[2,3-b]indoles

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2-Aryl-4-aroyl-9H-pyrido[2,3-b]indoles have been synthesised in good yields in a one-pot reaction involving Michael addition of 1,3-dihydro-3-[(2-oxo-2-aryl)ethylidene]-2H-indol-2-ones (I) to N-phenacylpyridinium bromides (II) in the presence of ammonium acetate and glacial acetic acid. Newly synthesized products have been characterised by IR, PMR,  $^{13}\text{C}$  NMR and mass spectral data.

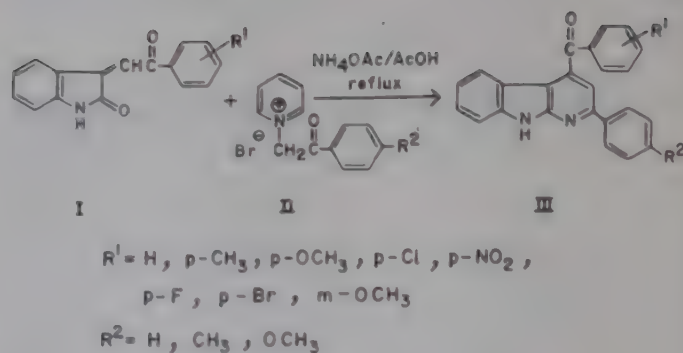
The 9H-pyrido[2,3-b]indole nucleus has interesting biological activities, in particular anticancer<sup>1</sup> and antibiotic<sup>2</sup> activities. Some methoxy derivatives are reported to possess luminescence properties<sup>3</sup> while others have been used as potential neoplasma inhibitors<sup>4</sup>. The synthesis of 9H-pyrido[2,3-b]indoles reported<sup>5-7</sup> so far suffer from several disadvantages; for example the starting precursors are either not easily available or difficult to synthesise. Further the scope of substitution in the two rings is limited and yields are generally low.

A facile synthesis of pyridine derivatives<sup>8</sup> involves Michael addition of N-phenacylpyridinium salt to  $\alpha,\beta$ -unsaturated ketones in acetic acid. The method till our recent publication<sup>9</sup> was applied either to the open chain  $\alpha,\beta$ -unsaturated ketones or to the carbocyclic rings incorporating this system<sup>10-13</sup>. We were the first to extend this approach using heterocyclic systems incorporating  $\alpha,\beta$ -unsaturated keto moiety in their framework and reported the synthesis of some interesting heterocyclic systems.

In this note we describe a one-pot synthesis of some 9H-pyrido[2,3-b]indole derivatives through the Michael addition to N-phenacylpyridinium bromides to easily synthesizable 1,3-dihydro-3-[(2-oxo-2-aryl)ethylidene]-2H-indol-2-ones (I).

Refluxing I with one equivalent of N-phenacylpyridinium bromide (II) and ammonium acetate in glacial acetic acid afforded the title compounds (III) (Scheme 1). The structure (III) for the synthesised compounds was further established by IR, PMR,  $^{13}\text{C}$  NMR and mass spectral data.

In contrast to the starting I, the products (III) in their IR, exhibited only one  $\nu\text{C}=\text{O}$  mode in the



Scheme 1

region 1760-1680  $\text{cm}^{-1}$ . The broad band in the region 3200-3070  $\text{cm}^{-1}$  could be attributed to  $\nu\text{NH}$  mode. In their PMR spectra, the compounds (III) displayed a characteristic doublet<sup>14</sup> in the downfield region at  $\delta 8.22$ -8.71 ppm, attributable to the aromatic 5-H. A broad singlet centred at  $\delta 8.66$ -11.53 could be assigned to N-H proton. Further, a singlet at  $\delta 6.14$ -6.83 which is slightly downfield as compared to the singlet of the methine proton of the precursors (I), could be assigned to the aromatic 3-H. However, in some cases it was not distinguishable from the multiplet shown by the other aromatic protons.

The  $^{13}\text{C}$  NMR spectra of IIIa, IIIc, IIIe and of 1,3-dihydro-3-[(2-oxo-2-aryl)ethylidene]-2H-indole-2-one (Ia) have been recorded. In Ia, two characteristic signals are observed at  $\delta 190.32$  and 167.46 ppm attributable to the carbonyl groups of the side chain and of cyclic imide group respectively. Compound IIIa displayed only one signal at  $\delta 189.50$  corresponding to the carbonyl group of the side chain while the signal due to imide carbonyl group of precursors disappeared. Further, a signal at  $\delta 109.60$  for the olefinic carbon of the side chain in I also disappeared in III. The mass spectral data of the representative compound (IIIa) provided further support to the assigned structure. In IIIa, instead of the molecular ion peak,  $\text{M}^+ + 1$  peak was observed. The ion at  $m/z$ , 170 corresponding to the benzylpyridinium cation forms the base peak in the spectrum.

Melting points determined on a Toshniwal melting point apparatus (capillary method) are uncorrected. IR spectra were recorded in KBr on a Perkin-Elmer 577 grating spectrophotometer ( $\nu_{\text{max}}$  in  $\text{cm}^{-1}$ ), PMR spectra in  $\text{CDCl}_3$  on a Jeol FX 90 Q (89.55 MHz) using TMS as internal standard (chemical shifts in  $\delta$ , ppm),  $^{13}\text{C}$  NMR on the same instrument and mass spectra on Hitachi model RMU 6E at 70 eV.

Table 1 — Characterisation Data of 2-Aryl-4-aryl-9H-pyrido[2,3-b]indoles

Compd	R <sup>1</sup>	R <sup>2</sup>	m.p. (°C)	Yield (%)	Mol. formula (M <sup>+</sup> + 1)	Found (%) (Calc.)		
						C	H	N
IIIa	H	H	270d	84	C <sub>24</sub> H <sub>16</sub> N <sub>2</sub> O	82.7 (82.8)	4.6 (4.6)	8.1 (8.0)
IIIb	H	CH <sub>3</sub>	240d	93	C <sub>25</sub> H <sub>18</sub> N <sub>2</sub> O	83.0 (82.9)	5.1 (5.0)	7.8 (7.7)
IIIc	H	OCH <sub>3</sub>	250d	94	C <sub>25</sub> H <sub>18</sub> N <sub>2</sub> O <sub>2</sub>	79.2 (79.4)	4.7 (4.8)	7.4 (7.4)
IIId	<i>p</i> -CH <sub>3</sub>	H	190	87	C <sub>25</sub> H <sub>18</sub> N <sub>2</sub> O	82.8 (82.9)	4.9 (5.0)	7.7 (7.7)
IIIe	<i>p</i> -OCH <sub>3</sub>	H	220d	77	C <sub>25</sub> H <sub>18</sub> N <sub>2</sub> O <sub>2</sub>	79.2 (79.4)	4.7 (4.8)	7.5 (7.4)
IIIf	<i>p</i> -Cl	H	260d	80	C <sub>24</sub> H <sub>15</sub> ClN <sub>2</sub> O	75.4 (75.3)	4.0 (3.9)	7.4 (7.3)
IIIg	<i>p</i> -NO <sub>2</sub>	H	> 290	62	C <sub>24</sub> H <sub>15</sub> N <sub>3</sub> O <sub>2</sub>	73.2 (73.3)	3.7 (3.8)	10.5 (10.7)
IIIh	<i>p</i> -F	H	280d	85	C <sub>24</sub> H <sub>15</sub> FN <sub>2</sub> O	78.8 (78.7)	4.1 (4.1)	7.7 (7.7)
IIIi	<i>p</i> -Br	H	285d	66	C <sub>24</sub> H <sub>15</sub> BrN <sub>2</sub> O	67.6 (67.4)	3.6 (3.5)	6.6 (6.6)
IIIj	<i>m</i> -OCH <sub>3</sub>	H	230d	94	C <sub>25</sub> H <sub>18</sub> N <sub>2</sub> O <sub>2</sub>	79.3 (79.4)	4.7 (4.8)	7.4 (7.4)

#### 2-Aryl-4-aryl-9H-pyrido[2,3-b]indoles: General procedure

A mixture of 1,3-dihydro-3-[(2-oxo-2-phenyl)ethylidene]-2H-indol-2-one<sup>15</sup> (I; 10 mmol) and N-phenacyl (or substituted phenacyl)pyridinium bromide (II; 10 mmol) was refluxed in acetic acid (8 ml) in the presence of ammonium acetate (6 g) for 2-4 hr. The reaction mixture was poured onto crushed ice, the resulting solid filtered, washed with water and recrystallized from isopropanol (Table 1). IR(KBr): 3120(NH), 1690(C=O); PMR (CDCl<sub>3</sub>): 6.87(*s*, 1H, C<sub>3</sub>-H), 7.15-8.01(*m*, 14H, Ar-H), 8.64(*d*, 1H, C<sub>5</sub>-H); <sup>13</sup>C NMR(DMSO): 181.50(C=O) and other aromatic carbons in expected region.

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## Synthesis of 1-Aryl-1,4-dihydro-2,4-diphenylimidazol-5(*H*)-ones

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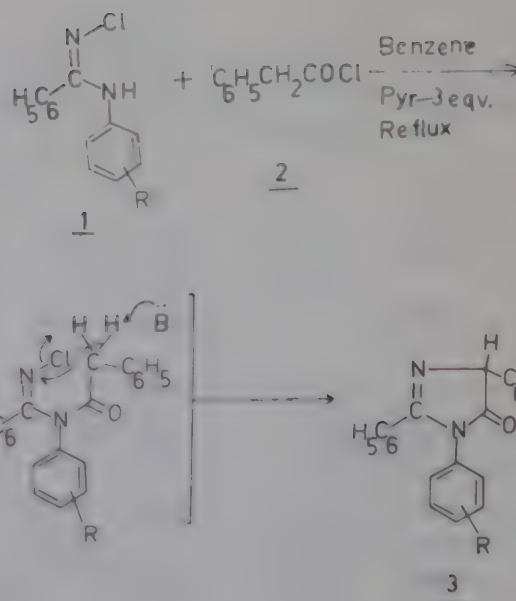
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The synthesis of 1-aryl-1,4-dihydro-2,4-diphenylimidazol-5(*H*)-ones (**3**) has been achieved by the reactions of *N*-chloro-*N'*-arylbenzamidines (**1**) with phenylacetyl chloride (**2**).

1,5-Dihydro-1,2,5-triphenylimidazol-4(*H*)-ones have become available recently<sup>1,2</sup>, the isomeric 1,4-dihydro-1,2,4-triphenylimidazol-5(*H*)-ones are still unknown. From this point of view the synthesis of the title compounds was felt desirable. The *N*-haloamidines which are known since long, have not been exploited much for the synthesis of heterocyclic compounds. As possible synthetic entry to the imidazol ring Stradi and coworkers have recently studied the reactions between *N*-haloamidines and various enamines<sup>3-6</sup>. We report herein an efficient synthetic approach towards the synthesis of title compounds using *N*-chloro-*N'*-arylbenzamidines.

Thus to a stirred solution of *N*-chloro-*N'*-phenylbenzamidine (**1**) (1.12g, 0.005 mol) and pyridine (1.18g, 0.015 mol) in dry benzene (20 ml) was added phenylacetyl chloride (0.77g, 0.005 mol) dropwise during 10 min, stirred at room temperature for 45 min and then refluxed in an oil-bath (80-90°C) for 2 hr.



The reaction mixture was washed with water 2×10 ml, dried (Na<sub>2</sub>SO<sub>4</sub>) and the solvent removed under reduced pressure. The residue thus obtained was treated with ether and the solid obtained was recrystallised from a mixture of 1:1 benzene-hexane to afford 1-aryl-1,4-dihydro-2,4-diphenylimidazol-5(*H*)-ones (**3**) in 60-85% yields.

The structure (**3**) for the products was assigned on the basis of analytical and spectral data (Table 1). The IR spectra of **3** exhibited  $\nu_{\text{C=O}}$  mode around 1780 cm<sup>-1</sup> and their PMR spectra displayed the methine proton as singlet around  $\delta$ 3.80 (1H). The appearance of  $\nu_{\text{C=O}}$  unexpectedly at higher wave number, finds analogy in literature<sup>7</sup> and is perhaps due to the fact the non-bonding electron pair at nitrogen attached to

Table 1—Aryl-1,4-dihydro-2,4-diphenylimidazole-5(*H*)-ones (**3**)<sup>a</sup>

Product <sup>b</sup>	R	Yield (%)	m.p. <sup>c</sup> (°C)	Mol formula (M <sup>+</sup> )	PMR ( $\delta$ ppm)
<b>3a</b>	H	80	163-65	C <sub>21</sub> H <sub>16</sub> N <sub>2</sub> O (312)	3.80 (s, 1H, methine), 7.10 (m, 15H, Ar-H)
<b>3b</b>	4-Cl	85	194-96	C <sub>21</sub> H <sub>15</sub> ClN <sub>2</sub> O (346)	3.80 (s, 1H, methine), 7.15 (m, 14H, Ar-H)
<b>3c</b>	4-CH <sub>3</sub>	65	180-81	C <sub>22</sub> H <sub>18</sub> N <sub>2</sub> O (326)	2.30 (s, 3H, CH <sub>3</sub> ), 3.90 (s, 1H, methine) 7.03 (m, 17H, Ar-H)
<b>3d</b>	4-Br	82	190-91	C <sub>21</sub> H <sub>15</sub> BrN <sub>2</sub> O	3.85 (s, 1H, methine), 7.30 (m, 14H, Ar-H)
<b>3e</b>	3-Cl	67	167-68	C <sub>21</sub> H <sub>15</sub> ClN <sub>2</sub> O	3.85 (s, 1H, methine), 7.20 (m, 15H, Ar-H)
<b>3f</b>	3-CH <sub>3</sub>	85	159-60	C <sub>22</sub> H <sub>18</sub> N <sub>2</sub> O	2.20 (s, 3H, CH <sub>3</sub> ), 3.70 (s, 1H, methine), 7.25 (m, 17H, Ar-H)

a) Common features in the IR spectra (KBr) of all the compounds: 3050, 2950 (C-H), 1780 (C=O) and 1620, 1580 cm<sup>-1</sup> (C=N, C=S)

b) Satisfactory microanalysis obtained; C,  $\pm 0.23$ ; H  $\pm 0.05$ ; N,  $\pm 0.03$ ;

c) Melting points reported are uncorrected.

C=O is engaged in delocalisation with aryl as well as C=N-functions which in turn increases the force constant of C=O bond. In addition six-membered lactams where C=O is attached to N-aryl have been found to absorb  $\sim 1740\text{ cm}^{-1}$  (ref. 8). Attempts are underway to synthesise **3** via an unambiguous route involving cyclisation of  $\text{PhNH-C(Ph)=N-CH(Ph)-COOR}$  as suggested by the reviewer.

N-Chloro-N'-arylbenzamidines (**1**) were obtained almost in quantitative yields by reacting N-chlorosuccinimide (0.105 mol) with N-arylbenzamidine in dry methylene chloride at room temperature<sup>5</sup>.

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## A New Synthesis of 3-Nitro-4*H*-pyran-4-ones from Acetylenic $\beta$ -Diketones†

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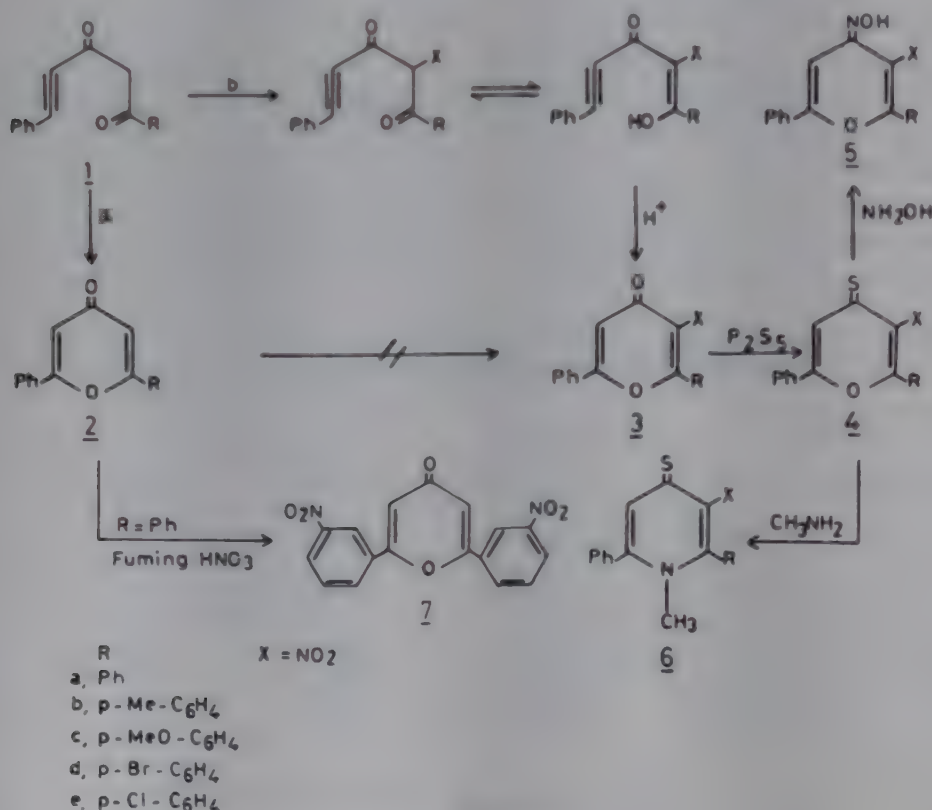
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A new method for the synthesis of 3-nitro-4*H*-pyran-4-ones is described involving nitration of acetylenic  $\beta$ -diketones. The 3-nitropyrones are converted into the corresponding 4-thiones which afford the respective 3-nitrooximes and *N*-methyl-4-thiopyridones on reaction with hydroxylamine and methylamine, respectively. The structures of the above compounds have been established by elemental analyses and spectral data.

Several nitro-substituted 4*H*-pyran-4-ones have been used recently as fungicidal<sup>1</sup>, insecticidal and miticidal<sup>2</sup> agents. Their synthesis is generally achieved by direct nitration of the pyranone ring<sup>3,4</sup>. Since only a few 4*H*-pyran-4-ones with nitro group in the nucleus

are reported in literature, it was thought desirable to synthesize more such compounds via a new route. In this note, a new method for the synthesis of 3-nitro-4-pyrones from acetylenic  $\beta$ -diketones<sup>5</sup> is described. Treatment of 1,5-diarylpent-1-yne-3, 5-diones (**1a-e**) with a 1:1 mixture (v/v) of nitric (d 1.41) and sulphuric (d 1.84) acids in gl. acetic acid gave 2, 6-diaryl-3-nitro-4*H*-pyran-4-ones (**3a-e**; X=NO<sub>2</sub>).

Since acetylenic  $\beta$ -diketones are easily cyclized to the corresponding 4*H*-pyran-4-ones<sup>5,6</sup>, the formation of 3-nitropyrones may proceed either (i) by cyclization of acetylenic  $\beta$ -diketones into the 4-pyrones (**2**) followed by nitration (path-a) or (ii) by initial nitration of acetylenic  $\beta$ -diketones and subsequent cyclization (path-b) (Scheme 1). To differentiate between the two possible routes, nitration of 2, 6-diaryl-4*H*-pyran-4-ones (**2a-e**) was attempted. However, these were recovered unchanged under the nitration conditions as used for acetylenic  $\beta$ -diketones. It is worth noting that 2, 6-diphenyl-4*H*-pyran-4-one (**2a**) underwent nitration in the phenyl residue when heated with fuming nitric acid in acetic acid, yielding 2, 6-di-(3-nitrophenyl)-4-



Scheme 1

†Part of this work was presented in the first Ibn Sina symposium of heterocyclic chemistry, held in 1986 at Cairo, Egypt, *Abstr.* p 111.

pyrone (7)<sub>7</sub>. These results exclude path-a for the formation of 3-nitro-4-pyrones.

No reports on the nitration of acetylenic  $\beta$ -diketones have been made earlier. However, it is generally assumed that halogenation of these compounds with iodine monochloride<sup>8a</sup>, NBS<sup>8b</sup> or N-chlorosuccinimide<sup>8c</sup> which leads to the corresponding 3-halogeno-4-pyrones proceeds via initial formation of 4-haloacetylenic  $\beta$ -diketones. Indeed in the case of NCS, 4-chloroacetylenic  $\beta$ -diketones could be isolated<sup>8c</sup>.

The IR spectra of 3-nitro-4-pyrones (3; Table 1) exhibited the carbonyl absorption at 1685-1715 as well as nitro band at 1335-1355 and 1520-1545  $\text{cm}^{-1}$  (ref. 9).

It has been noticed that the carbonyl absorption of 3-substituted 2, 6-diaryl-4H-pyran-4-ones depends on the nature of the substituent at position-3. The  $\nu\text{C=O}$  was found to decrease in the order  $\text{NO}_2 > \text{H} > \text{Cl} > \text{Br} > \text{I} > \text{OH}$  (Table 2).

The PMR spectra of 3 displayed a singlet at  $\delta$  7.03-7.27 for the proton at C-5. It was observed that the presence of strong electron-attracting groups ( $\text{NO}_2$ ) at position-3 of the pyrone ring resulted in a downfield shift of the C<sub>5</sub>-proton, while electron-releasing groups (OH) produced the opposite effect (Table 3).

Treatment of 3a-e with  $\text{P}_2\text{S}_5$  afforded the corresponding 2, 6-diaryl-3-nitro-4H-pyran-4-thiones (4a-

Table 1 — Characterization Data of 3-Nitro-4-pyrone Derivatives (3-6)

Compd	m.p. °C	Mol. Formula	Found (%)		Calc.*	PMR (CDCl <sub>3</sub> ) <sup>†</sup> $\delta$ , ppm			
			N	S		H-5 (S)	Ar-H (m)	N-CH <sub>3</sub>	Others (S)
3a	160	C <sub>17</sub> H <sub>11</sub> NO <sub>4</sub>	4.7 (4.8)	—	— (5)	7.03	8.24		
3b	165	C <sub>18</sub> H <sub>13</sub> NO <sub>4</sub>	4.5 (4.6)	—	— (—)	7.08	8.15		2.40 (CH <sub>3</sub> )
3c	195	C <sub>18</sub> H <sub>13</sub> NO <sub>3</sub>	4.2 (4.3)	—	— (—)	7.10	8.14		3.97 (OCH <sub>3</sub> )
3d	197	C <sub>17</sub> H <sub>10</sub> NBrO <sub>4</sub>	3.8 (3.8)	—	21.9 (21.5)	7.27	8.15		
3e	175	C <sub>17</sub> H <sub>10</sub> NClO <sub>3</sub>	4.2 (4.3)	—	10.4 (10.8)	7.04	8.27		
4a	140	C <sub>17</sub> H <sub>11</sub> NO <sub>3</sub> S	4.7 (4.5)	10.1 (10.4)	— (—)		7.70		
4b	155	C <sub>18</sub> H <sub>13</sub> NO <sub>3</sub> S	4.1 (4.3)	9.7 (9.9)	— (—)		7.57		2.33 (CH <sub>3</sub> )
4c	160	C <sub>18</sub> H <sub>13</sub> NO <sub>4</sub> S	4.3 (4.1)	9.6 (9.4)	— (—)		7.62		3.99 (OCH <sub>3</sub> )
4d	135	C <sub>17</sub> H <sub>10</sub> NBrO <sub>3</sub> S	3.4 (3.6)	8.6 (8.3)	20.2 (20.6)		7.50		
4e	145	C <sub>17</sub> H <sub>11</sub> NClO <sub>3</sub> S	4.0 (4.1)	9.0 (9.3)	10.6 (10.3)		7.69		
5a	212	C <sub>17</sub> H <sub>12</sub> N <sub>2</sub> O <sub>4</sub>	9.0 (9.1)	—	— (—)	6.64		7.80	
5b	210	C <sub>18</sub> H <sub>14</sub> N <sub>2</sub> O <sub>4</sub>	8.9 (8.7)	—	— (—)	6.63		7.77	2.30 (CH <sub>3</sub> )
5c	215	C <sub>18</sub> H <sub>14</sub> N <sub>2</sub> O <sub>3</sub>	8.5 (8.3)	—	— (—)	6.58		7.30	3.80 (OCH <sub>3</sub> )
5d	220	C <sub>17</sub> H <sub>11</sub> N <sub>2</sub> BrO <sub>4</sub>	7.0 (7.2)	—	20.3 (20.7)	6.63		7.35	
5e	230	C <sub>17</sub> H <sub>11</sub> N <sub>2</sub> ClO <sub>4</sub>	8.4 (8.2)	—	10.9 (10.4)	6.60		7.38	
6a	165	C <sub>18</sub> H <sub>14</sub> N <sub>2</sub> O <sub>2</sub> S	8.9 (8.7)	9.8 (9.9)	— (—)	6.50	3.40	7.39	
6b	190	C <sub>19</sub> H <sub>16</sub> N <sub>2</sub> O <sub>2</sub> S	8.1 (8.3)	9.3 (9.5)	— (—)	6.53	3.50	7.32	2.34 (CH <sub>3</sub> )
6c	200	C <sub>19</sub> H <sub>16</sub> N <sub>2</sub> O <sub>3</sub> S	8.0 (8.0)	9.3 (9.1)	— (—)	6.80	3.60	7.90	3.80 (OCH <sub>3</sub> )
6d	195	C <sub>18</sub> H <sub>13</sub> N <sub>2</sub> BrO <sub>2</sub> S	7.2 (7.0)	7.8 (8.0)	20.3 (20.0)	6.79	3.59	7.82	

\*Satisfactory analyses were obtained for C and H for all the compounds.

<sup>†</sup>The PMR spectra of 5a-e were recorded in DMSO-*d*<sub>6</sub>.

Table 2—Carbonyl Frequencies of 3-Substituted 2, 6-Diaryl-4-pyrones (3)

Compd X=	$\nu\text{C=O}$ ( $\text{cm}^{-1}$ )					
	$\text{NO}_2$	H	$\text{Cl}^{\text{bc}}$	$\text{Br}^{\text{bb}}$	$\text{I}^{\text{ba}}$	$\text{OH}^{\text{12}}$
3a	1715	1650	1644	1643	1615	1595
3b	1715	1644			1600	1593
3c	1710	1642		1623	1619	1591
3d	1690	1658	1641	1620	1624	1606
3e	1685	1657	1660	1650	1624	1623

Table 3—Chemical Shifts (in  $\delta$ , ppm) of  $\text{C}_5$ -Proton of 3-Substituted 2, 6-Diaryl-4-pyrones (3)

Compd X=	$\text{C}_5$ -Proton		
	$\text{NO}_2$	$\text{H}^{\text{5}}$	$\text{OH}^{\text{12}}$
3a	7.03	6.92	6.77
3b	7.08	6.72	6.37
3c	7.10	6.78	6.34
3d	7.27	6.67	6.57
3e	7.04	6.75	

e). The latter were converted into the respective oximes (5a-e) and N-methyl-4-thiopyridones (6a-d) on reaction with hydroxylamine and aq. methylamine, respectively (Scheme 1).

The IR spectra of the thiopyrones (4) exhibited the thiocarbonyl absorption at 1115-1130, the oximes (5) showed a  $\text{C=N}$  band at 1660-1665, while the thiopyridones (6) showed the  $\text{C=S}$  band at 1110-1120  $\text{cm}^{-1}$  (Table 1). The signal for the  $\text{C}_5$ -proton of 4 overlapped with that for aromatic protons in their PMR spectra. The observed deshielding is expected due to the presence of  $\text{C=S}$  group<sup>10</sup>. In the case of oximes (5) and the thiopyridones (6) the  $\text{C}_5$ -proton resonated at  $\delta$  6.58-6.64 and 6.50-6.80, respectively (Table 1).

IR spectra were recorded in KBr on a Unicam SP 1025 spectrophotometer, and PMR spectra on a Varian EM-390 90 MHz spectrometer using TMS as internal standard.

#### 2-Aryl-3-nitro-6-phenyl-4H-pyran-4-ones (3; Table 1)

A mixture of nitric (d 1.41; 2 ml) and sulphuric acids (d 1.84; 2 ml) in gl. acetic acid (6 ml) was gradually added to a suspension of 1a-e (0.5 g; 0.0020 mol) in gl. acetic acid (6 ml) in a large tube with shaking. The tube was then cautiously warmed over a small flame and as soon as brown fumes were observed, the tube was immersed in crushed ice with stirring for 3 hr. The

reaction mixture was poured into cold water (30 ml) with stirring. The yellow precipitate was filtered, washed with cold water, dried and crystallized from methanol in yellow needles, yield 82-90%.

#### 2-Aryl-3-nitro-6-phenyl-4H-pyran-4-thiones (4; Table 1)

These were prepared from the respective 3-nitro-4H-pyran-4-ones (3) by the action of  $\text{P}_2\text{S}_5$  as described earlier<sup>11</sup>.

#### 2-Aryl-3-nitro-6-phenyl-4H-pyran-4-one oximes (5; Table 1)

These were prepared from the corresponding 3-nitro-4H-pyran-4-thiones (4) and hydroxylamine hydrochloride and sodium acetate in ethanol as described earlier<sup>11</sup>.

#### 2-Aryl-1-methyl-3-nitro-6-phenyl-4-thiopyridones (6; Table 1)

A solution of 4 (0.5 g; 0.0017 mol) in ethanol (15 ml) and 33% aq. methylamine solution (5 ml) was refluxed for 8-10 hr. The alcohol was evaporated under reduced pressure and the separated thiopyridone crystallized from ethanol in yellow needles, yield 65-80%.

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# Synthesis of 2-Aryl-7-methylpyrano[4, 3-*b*]-pyran-4 (*H*), 5(*H*)-diones

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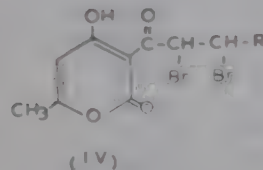
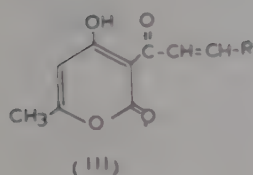
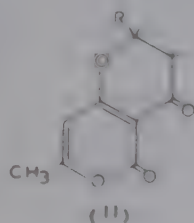
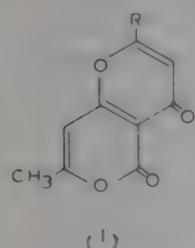
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3-Cinnamoyl-4-hydroxypyran-2(*H*)-ones (IIIa-e) on bromination give the corresponding bromo derivatives (IVa-e) in quantitative yields. These bromo derivatives (IVa-e) on heating with pyridine containing few drops of piperidine give 2-aryl-7-methylpyrano[4, 3-*b*]pyran-4(*H*), 5(*H*)-diones (Ia-e) in 60-70% yields. This method is of general applicability.

A number of methods are available for the synthesis of pyranopyran-4, 5-diones of the type I(R=alkyl)<sup>1-3</sup>. However, these methods suffer from lack of general applicability. In view of the synthetic importance and the utility of these compounds in the study of biogenetic type synthesis<sup>4</sup> of phenolic compounds, we describe herein a simple and general method for the synthesis of 2-aryl-7-methylpyrano[4, 3-*b*]pyran-4(*H*), 5(*H*)-diones (I).

Analogous to the condensation of aliphatic aldehydes with dehydroacetic acid to form 2, 3-dihydro-pyranopyran-4, 5-diones (II, R=alkyl)<sup>5</sup>, our initial attempts to condense aromatic aldehydes with dehydroacetic acid resulted in the formation of cinnamoyl derivatives (III), instead of the anticipated II(R=aryl). The failure of III to undergo cyclisation to furnish II via Michael-type addition reaction is attributable to the conjugative effect<sup>6</sup> of the phenyl group. The problem was solved by converting III into their



I, III, IV	R
a	Ph
b	2-Cl. Ph
c	4-NO <sub>2</sub> . Ph
d	4-MeO. Ph
e	4-EtO. Ph

Table 1—Formation of Ia-e from IVa-b

Comp	IV*		I*	
	m.p(°C)	Yield(%)	m.p(°C)	Yield(%)
a	152	95	265	60
b	80	95	160	60
c	110	100	170	75
d	150	95	215	65
e	180	100	180	60

\*All the compounds gave satisfactory C,H analyses.

corresponding bromo derivatives (IV) which on heating with pyridine in the presence of catalytic amount of piperidine gave the desired (Ia-e) in good yields.

The identity of the products was established on the basis of their spectral data. Compounds(I) exhibited carbonyl absorptions in the regions 1720-1750 and 1620-1640 cm<sup>-1</sup> respectively, for the 2-pyrone and 4-pyrone rings. PMR spectra in TFA gave signals at  $\delta$ 7-7.4 (aromatic), 5.9-6.2 (2H) and 2.3 (3H) for the protons at 2,3/8 and 7-positions respectively.

## 2-Aryl-7-methylpyrano[4, 3-*b*]pyran-4(*H*), 5(*H*)-diones (I): General procedure

3-Cinnamoyl derivatives (III) were prepared by the method given in literature<sup>7</sup>. Addition of bromine (0.003 mol) to a solution of III (0.003 mol) in chloroform (10-15 ml) at 0°C followed by evaporation of the solvent gave bromo derivatives (IVa-e) in 95-100% yields (Table I).

A mixture containing appropriate (IV, 1 g), benzene (5 ml), pyridine (5 ml) and piperidine (1-2 drops) was refluxed (1-1.5hr). Concentration of the reaction mixture under reduced pressure led to Ia-e in 60-70% yields (Table I). The same products (Ia-e) were also obtained but in diminished yields by refluxing (1 hr) IV in pyridine and then adding the reaction mixture to dil hydrochloric acid.

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# Ac<sub>2</sub>O/Et<sub>3</sub>N Induced Condensation of *o*-Hydroxybenzophenone with Phenylacetic Acid: A Study of the Mechanism of Coumarin Formation†

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The mechanism of coumarin formation from *o*-hydroxybenzophenone and phenylacetic acid in the presence of Ac<sub>2</sub>O/Et<sub>3</sub>N has been investigated. Intermolecular hydrogen bonding of *o*-hydroxy leads to partial carbonium ion formation thereby facilitating nucleophilic attack by the active methylene of phenylacetic acid. A subsequent attack by the lone pair on *o*-hydroxy results in the formation of the probable intermediate III which undergoes dehydration to form coumarin.

Synthesis of coumarins by condensing *o*-hydroxybenzophenones with phenylacetic acid in the presence of triethylamine and acetic anhydride is a standard procedure<sup>1</sup>. However, it is not well documented whether coumarin formation proceeds via initial ester formation and subsequent attack of active methylene on the benzophenone carbonyl or vice-versa or both the steps go together in a concerted manner. A study of the *o*-hydroxy group in benzophenone in the formation of coumarin which is reported here.

2-Hydroxy-5-methylbenzophenone<sup>2</sup> (**1**) when re-

fluxed with an equimolar amount of phenylacetic acid in the presence of acetic anhydride and triethylamine for 30 min gave a mixture of 5-methyl-2-phenylacetoxybenzophenone (**2**) and 6-methyl-3,4-diphenyl coumarin (**3**)<sup>1</sup> (Table I) which were isolated by careful column chromatography over silica gel and characterised by their IR and PMR data. The conversion of **1** into the coumarin (**3**) was found to be complete in 3 hr. A faster condensation was observed when acetic anhydride was replaced by propionic anhydride.

Formation of the ester **2** suggests its involvement as an intermediate during coumarin formation. This presumption was also supported by the observation that the unsubstituted benzophenone (**4**) when treated with phenylacetic acid under similar conditions in propionic anhydride gave only traces of **2**, **3**, 3-triphenyl-2-propenoic acid (**5**) after 5 days of refluxing as characterised by its IR and mass spectral data [IR (neat): 1715 cm<sup>-1</sup>; MS: *m/z* 300 (M<sup>+</sup>)]. This shows that an initial attack of the active methylene on the benzophenone carbonyl is not a facile reaction. However, when ester **2** (prepared by reacting **1** with phenylacetyl chloride) was refluxed with Ac<sub>2</sub>O/Et<sub>3</sub>N, it was converted into **3** in only 53.7% yield after 20 hr of reflux. The period of reflux was reduced to 6 hr when propionic anhydride was used in place of Ac<sub>2</sub>O.

Similarly, 2, 4'-dihydroxy-4-methoxybenzophenone<sup>1</sup> (**6**) when refluxed with phenylacetic acid in Ac<sub>2</sub>O/

Structure	Compd No	R <sup>1</sup>	R <sup>2</sup>	R <sup>3</sup>	R <sup>4</sup>
	1	H	H	CH <sub>3</sub>	H
	2	H	H	CH <sub>3</sub>	H
	3	H	H	CH <sub>3</sub>	H
	4	H	H	H	H
	5	H	H	H	H
	6	H	OCH <sub>3</sub>	OH	OH
	7	H	OCH <sub>3</sub>	OCOCH <sub>3</sub>	OCOCH <sub>3</sub>
	8	H	OCH <sub>3</sub>	OCH <sub>3</sub>	H
	9	H	OCH <sub>3</sub>	OH	NO <sub>2</sub>
	10	CH <sub>3</sub>	H	H	H
	11	H	OCH <sub>3</sub>	OCOCH <sub>3</sub>	H
	12	H	OCH <sub>3</sub>	OCOC <sub>2</sub> H <sub>5</sub>	H

Table I—Reactions of Benzophenones with Phenylacetic Acid under Different Conditions

Compd	Solvent	Reaction period (hr)	Product	Yield (%)
1	Ac <sub>2</sub> O	1/2	2+3	30, 28 respectively
1	Ac <sub>2</sub> O	3	3	65
1	Propionic anhydride	<3	3	65
2	Ac <sub>2</sub> O	20	3	53.7
2	Propionic anhydride	6	3	53
4	Propionic anhydride	5 days	5	Traces
6	Ac <sub>2</sub> O	3-4	7	
8	Ac <sub>2</sub> O	16	7	5-10
8	Propionic anhydride	62	9	40
10	Propionic anhydride	20	10	—
11	Propionic anhydride	20	11	

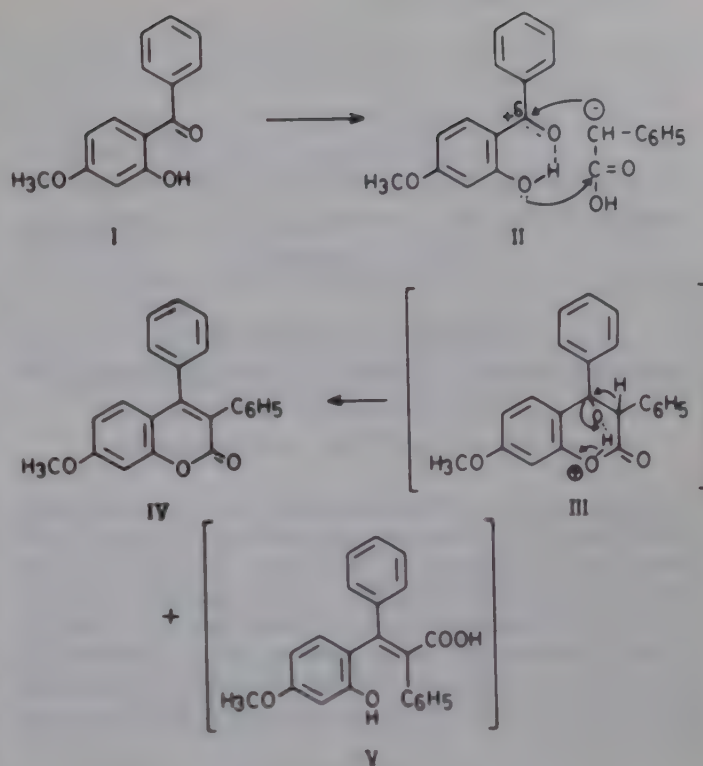
† CDRI Communication No. 3988

Et<sub>3</sub>N afforded 4-(*p*-acetoxyphenyl)-7-methoxy-3-phenylcoumarin<sup>1</sup> (7) in only 3 hr, whereas 2,4'-diacetoxy-4-methoxybenzophenone (8) [m.p. 110°, IR: 1760 (OAc), 1640 cm<sup>-1</sup> (C=O)] under similar conditions gave 7 in only 5-10% yield after 10 hr of reflux. Blocking of hydroxyl group in the second case as acetate interferes with coumarin formation. At a higher temperature in refluxing propionic anhydride, 40% condensation could be achieved in 6 hr to give 7-methoxy-3-phenyl-4-(*p*-propyloxyphenyl) coumarin (9) [m.p. 159°, IR: 1745 (COC<sub>2</sub>H<sub>5</sub>), 1700 cm<sup>-1</sup> (C=O)]. The above observation clearly indicates that the intermediate product in coumarin formation cannot be 2 which would have required a lesser period of reflux as compared to the corresponding hydroxybenzophenone.

When 2, 4-dimethoxybenzophenone<sup>3</sup> (10) was refluxed with phenylacetic acid in propionic anhydride/Et<sub>3</sub>N, it remained unchanged even after 10 hr. It indicates that electron donation from *ortho* and *para* substituents is not sufficient to activate the carbonyl function of benzophenone for condensation with the active methylene of phenylacetic acid.

It would therefore appear from the above discussion that the anchimeric assistance by *ortho*-hydroxyl group through hydrogen bond formation inducing partial polarisation of the carbonyl function (a partial carbonium ion formation) is necessary for condensation. A subsequent attack by the lone pair on *o*-hydroxyl group results in the formation of the probable intermediate III (Scheme 1) which undergoes dehydration to give the coumarin.

2-Hydroxy-4-methoxy-4'-nitrobenzophenone<sup>4</sup> (11) when refluxed with phenylacetic acid in Ac<sub>2</sub>O/Et<sub>3</sub>N, remained unchanged even after 20 hr of reflux. The presence of electron withdrawing nitro group at *para*-position interferes with the hydrogen bond formation by reducing the nucleophilicity of *o*-hydroxy group and hence with the condensation reaction. Involvement of intermediate III would explain almost quantitative (>75%) formation of coumarin instead of an equilibrium mixture of coumarin and the acid V (M<sup>+</sup> 346).



Scheme - 1

When ester 2 was refluxed with Ac<sub>2</sub>O and Et<sub>3</sub>N in the presence of a catalytic amount of phenol for 3 hr, partial cyclization of 2 occurred and a mixture of 2 and 3 was obtained. Complete cyclisation occurred after refluxing by propionic anhydride, 2 was converted into 3 in 3 hr. This suggests that phenol provides the required polarisation of the benzophenone carbonyl through intermolecular hydrogen bonding.

Preparation of the benzophenones and their condensation with phenylacetic acid were carried out according to the method reported earlier<sup>1</sup>.

All the compounds reported gave the expected IR and PMR data and analysed satisfactorily for their C, H and N contents.

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## Condensation of Cuprous Phenylacetylide with *o*-Bromohydroxyxanthenes: Synthesis of Furoxanthenes

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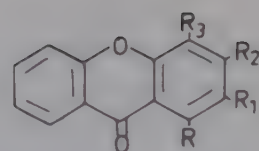
2-Bromo-1-hydroxy-3-methylxanthone (1), 2-bromo-1-hydroxyxanthone (3), 4-bromo-3-hydroxyxanthone (5) and 2,4-dibromo-3-hydroxyxanthone (7) have been condensed with cuprous phenylacetylide in pyridine under nitrogen atmosphere to give 4-methyl-2-phenyl-11*H*-furo[1,2-*b*]xanthone (2), 2-phenyl-11*H*-furo[1,2-*b*]xanthone (4), 2-phenyl-6*H*-furo[3,4-*b*]xanthone (6) and 4-bromo-2-phenyl-6*H*-furo[3,4-*b*]xanthone (8) respectively. Their structures have been confirmed by PMR and mass spectra.

In continuation of our work on the synthesis of furoxanthenes<sup>1,2</sup>, we report herein the synthesis of furoxanthenes (2,4,6 and 8) by the condensation of cuprous phenylacetylide with 2-bromo-1-hydroxy-3-methyl-(1), 2-bromo-1-hydroxy-(3), 4-bromo-3-hydroxy-(5) and 2,4-dibromo-3-hydroxy-(7)-xanthenes respectively.

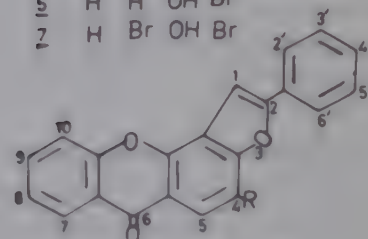
Coupling of cuprous phenylacetylide with 1 by refluxing in pyridine under N<sub>2</sub> atmosphere led to 4-methyl-2-phenyl-11*H*-furo[1,2-*b*]xanthone (2), the structure of which was confirmed by its mass and PMR spectral data. PMR spectrum (CDCl<sub>3</sub>) is indicative of absence of OH proton. It exhibited a one-proton singlet each at  $\delta$  6.99 and 7.4 assignable to H-3 and H-5 respectively. The *peri*-proton, H-10 appeared as a doublet at  $\delta$  8.3 (*J* = 9, 2 Hz); H-2' and H-4' appeared at 7.97 (*dd*, *J* = 9, 2 Hz); H-8 appeared at 7.65 (*td*, *J* = 9, 9 Hz); a five-proton multiplet could be assigned to H-3', H-4', H-5', H-7 and H-9; and CH<sub>3</sub> protons appeared as a sharp singlet at 2.55.

Similarly, condensation of 2-bromo-1-hydroxyxanthone (3), 4-bromo-3-hydroxyxanthone (5) and 2,4-dibromo-3-hydroxyxanthone (7) with cuprous phenylacetylide gave 2-phenyl-11*H*-furo[1,2-*b*]xanthone (4), 2-phenyl-6*H*-furo[3,4-*b*]xanthone (6) and 4-bromo-2-phenyl-6*H*-furo[3,4-*b*]xanthone (8) respectively, structures of all products were confirmed by mass and PMR data (Table 1).

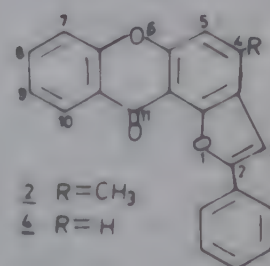
PMR spectra were recorded on Perkin-Elmer R-32 (90 MHz) and R-34 (220 MHz) spectrometers using



	R	R <sub>1</sub>	R <sub>2</sub>	R <sub>3</sub>
1	OH	Br	CH <sub>3</sub>	H
3	OH	Br	H	H
5	H	H	OH	Br
7	H	Br	OH	Br



6	R = H
8	R = Br



2	R = CH <sub>3</sub>
4	R = H

Table 1—Physical Data of Compounds 2, 4, 6 and 8

Compound	m.p. °C	Mol. formula (M <sup>+</sup> )	Found (Calc.) %		PMR(CDCl <sub>3</sub> ) $\delta$ ppm
			C	H	
2	210	C <sub>22</sub> H <sub>14</sub> O <sub>3</sub> (326)	80.5 (80.7)	4.5 (4.6)	—
4	165	C <sub>24</sub> H <sub>12</sub> O <sub>3</sub>	81.0 (80.8)	3.6 (3.9)	7.2-8.0 ( <i>m</i> , 10H, H-3 and aromatic protons) 6.83 ( <i>d</i> , 1H, <i>J</i> = 9 Hz, H-4) 8.32 ( <i>dd</i> , 1H, <i>J</i> = 9 Hz, H-10)
6	235	C <sub>21</sub> H <sub>12</sub> O <sub>3</sub> (312)	80.9 (80.8)	4.2 (3.9)	7.4-7.8 ( <i>m</i> , 10H, H-1 and aromatic protons) 8.25 ( <i>d</i> , 1H, <i>J</i> = 9 Hz, H-5) 8.4 ( <i>dd</i> , 1H, <i>J</i> = 8, 2 Hz, H-7)
8	240	C <sub>21</sub> H <sub>11</sub> O <sub>3</sub> Br (392)	64.7 (64.5)	3.1 (2.8)	7.4-7.8 ( <i>m</i> , 6H, H-1, H-8, H-10, H-3', H-4' and H-5') 7.93 ( <i>d</i> , 2H, <i>J</i> = 9 Hz, H-2' and H-6') 8.39 ( <i>s</i> , 1H, H-5) 8.43 ( <i>s</i> , 1H, H-7)

TMS as an internal standard and mass spectra on an AEI MS12 machine.

#### *General procedure*

A mixture of cuprous phenylacetylide<sup>3</sup> (0.002 mol) and bromohydroxyxanthone (0.002 mol) in pyridine was refluxed under nitrogen atmosphere for 7 hr. The reaction mixture after cooling was poured into cold dil hydrochloric acid (1:1). The separated solid was filtered off and purified to give furoxanthone.

We sincerely thank the UGC, New Delhi, for the award of a research fellowship to one of us (GNP) and Dr F M Dean, Department of Organic Chemistry, University of Liverpool, England for PMR spectra.

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## Condensation Product of Salicylaldehyde & 2-Bromo-2'-hydroxyacetophenone: Revision of Structure

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Reaction between salicylaldehyde and 2-bromo-2'-hydroxyacetophenone (1) gives 2-(2-hydroxybenzylidene)coumaran-3-one (5) rather than 2-(2-hydroxybenzoyl)benzofuran (2) as reported in a patented literature.

In connection with our work on oxygen heterocycles, we required 2-(2-hydroxybenzoyl)benzofuran (2). The reported synthesis of 2 (m.p. 170°), which is patented<sup>1</sup>, involved condensation of salicylaldehyde with 2-bromo-2'-hydroxyacetophenone (1) in the presence of alkali. Instead of using highly lachrymetic 1, we looked for a convenient synthesis of 2.

In our approach we envisaged that Fries rearrangement of phenyl coumarilate (3) in the presence of anhydrous aluminium chloride should result in the formation of 2. Usual work-up of reaction mixture of the rearrangement afforded a yellow coloured compound, m.p. 64°. Its mode of formation, PMR [ $\delta$  12.0 (1H, s, D<sub>2</sub>O exchangeable), 8.4 (1H, dd), 7.8-6.8 (8H, m)] and, IR (1630 cm<sup>-1</sup>) data and elemental analyses suggested it to be 2 (Scheme 1). However, the product reported in literature<sup>1</sup> and that obtained by us differed in their melting points. This prompted us to repeat the reported condensation reaction<sup>1</sup> between salicylaldehyde and 1. Direct crystallisation of the reaction product from CHCl<sub>3</sub>/EtOH gave the pure compound which melted at 234° instead of 170°<sup>1</sup>. The PMR spectrum of literature product was reported to display a one proton singlet at  $\delta$  10.0 for the chelated OH (exchangeable with D<sub>2</sub>O) while the PMR spectrum of the product synthesized by us displayed the OH proton at  $\delta$  12.0.

We believe that the literature product is the aurone (5) formed by the initial intramolecular attack of OH in 1 leading to formation of coumaran-3-one (4) rather than 2. Compound 4 then easily condenses with salicylaldehyde to give the aurone (5) (Scheme 2).

To confirm the formation of the aurone (5) and not 2 in the reported reaction<sup>1</sup>, the bromoketone (1) was first converted into 4<sup>2</sup> and then condensed with salicylaldehyde under the same conditions (KOH/EtOH). Work-up afforded 5 which was found to be identical in

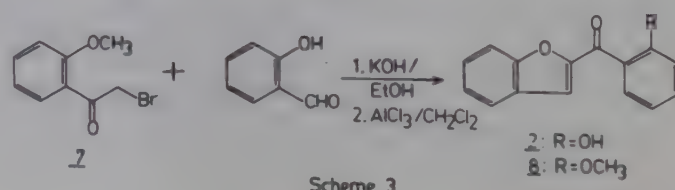
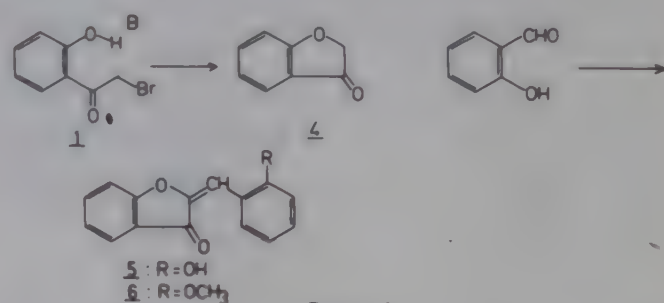
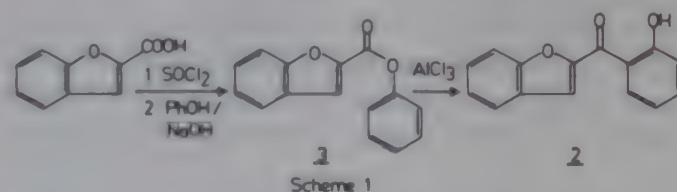
every respect (m.p., m.m.p., co-IR) with the compound obtained by the earlier reported reaction<sup>1</sup>. Further transformation into its methyl ether (6), m.p. 175° (lit.<sup>3</sup> m.p. 175°), using (CH<sub>3</sub>)<sub>2</sub>SO<sub>4</sub>-K<sub>2</sub>CO<sub>3</sub>-acetone method also confirmed its structure as the aurone (5).

Thus the formation of 5 and not 2 is due to the presence of free hydroxyl group in 1. In order to achieve the synthesis of the required 2, we modified the literature methodology<sup>1</sup>. Instead of using 1, we used the corresponding methyl ether (7) to avoid the formation of 4 (Scheme 3). Condensation of 7 with salicylaldehyde, as reported<sup>1</sup>, led to a product, m.p. 64°, identical with 2, obtained by us by the Fries rearrangement of phenyl coumarilate (3). This shows that the desired benzofuran melts at 64° and not at 170° as reported<sup>1</sup>.

Melting points are uncorrected. IR spectra were recorded in nujol on a Perkin-Elmer model-337 IR spectrophotometer and PMR spectra on a 90MHz Perkin-Elmer R-32 instrument using TMS as an internal standard (chemical shifts in  $\delta$ , PPM).

### Phenyl coumarilate (3)

A mixture of coumarilic acid (2.6 g, 0.016 mol) and freshly distilled thionyl chloride (5 ml) was refluxed for 1 hr. Excess of thionyl chloride was removed under reduced pressure. To the acid chloride thus obtained, m.p. 60°, was added a solution of phenol (1.6 g, 0.016 mol) in sodium hydroxide (9 ml, 10%). The resulting mixture was shaken vigorously, the precipitated solid



filtered, washed with dil. sodium hydroxide, water and dried. Crystallisation from hexane-benzene gave **3** as white crystals, m.p. 100-101°, yield 3.6 g (94%) (Found: C, 75.5; H, 4.1.  $C_{15}H_{10}O_3$  requires C, 75.6; H, 4.2%); IR: 1750 (C=O); PMR ( $CDCl_3$ ): 7.8-7.1 (*m*, Ar-H).

#### 2-(2-Hydroxybenzoyl)benzofuran (2)

An intimate mixture of finely powdered anhydrous aluminium chloride (1 g, 0.0075 mol) and **3** (1 g, 0.0042 mol) was heated in an oil-bath at 130-135° for 2 hr, and decomposed with cold dil hydrochloric acid (1:1). The oily product formed was extracted with ether, the ether layer washed with water, aq sodium bicarbonate (10%), water and dried ( $Na_2SO_4$ ). Removal of solvent gave a residue which on column chromatography using hexane-benzene (1:1) followed by crystallisation from aq ethanol gave **2** as yellow needles, m.p. 64°, yield 0.77 g (77%) (Found: C, 75.4; H, 4.1  $C_{15}H_{10}O_3$  requires C, 75.6; H, 4.2%); IR 1630 (C=O) PMR ( $CDCl_3$ ): 12.0 (1H, *s*, Ar-OH, exchangeable with  $D_2O$ ), 8.4 (1H, *dd*,  $J=9Hz$ , 2Hz, benzoyl-6-H), 7.8-6.8 (8H, *m*, Ar-H).

#### 2-(2-Hydroxybenzylidene) coumaran-3-one (5)

To a hot solution of salicylaldehyde (1 g, 0.008 mol) in alcoholic potassium hydroxide (0.5 g in 15 ml ethanol) was added, dropwise, a solution of **1** (1.7 g, 0.008 mol) in ethanol (5 ml). The resulting mixture was refluxed for 2 hr and the solvent removed. The residue was acidified, the precipitated solid filtered, washed with water and dried. Crystallisation from chloroform-ethanol gave **5** as yellow needles, m.p. 234°, yield 1.4 g (75%) (Found: C, 75.4; H, 4.1.  $C_{15}H_{10}O_3$  requires C, 75.6; H, 4.2%) IR: 3100 (OH), 1700 (C=O); PMR ( $CDCl_3 + DMSO-d_6$ ): 10.0 (1H, *bs*, Ar-OH, exch with

$D_2O$ ), 8.21 (1H, *dd*,  $H=9Hz, 2Hz$ , 4-H), 7.9-6.9 (8H, *m* Ar-H and =CH-).

#### 2-(2-Methoxybenzoyl)benzofuran (8)

To a hot solution of salicylaldehyde (0.5 ml, 0.004 mol) in alcoholic potassium hydroxide (0.22 g, in 2 ml ethanol) was added, dropwise, a solution of **7** (0.9 g, 0.004 mol) in ethanol (2 ml). The reaction mixture was then refluxed for 2 hr. Usual work-up gave **8** as a thick viscous oil, yield 0.51 g (52%). It was used directly for demethylation; PMR ( $CDCl_3$ ): 7.8-6.9 (9H, *m* Ar-H), 3.8 (3H, *s*, Ar-OCH<sub>3</sub>).

#### 2-(2-Methoxybenzoyl)benzofuran (2)

To a stirred suspension of anhydrous aluminium chloride (0.5 g, 0.003 mol) in dry dichloromethane (10 ml) was added a solution of **8** (0.4 g, 0.001 mol) in dry dichloromethane (5 ml). The resulting mixture was stirred for 2 hr at room temperature. Usual work-up followed by column chromatography using hexane-benzene (1:1) gave **2** as a yellow compound, m.p. and m.m.p. 64°, yield 0.22 g (58%).

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## Halolactonisation of 2-Alkynylbenzoic Acids

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Halosubstituted isocoumarins(II) are readily obtained by the halolactonisation reaction of 2-alkynylbenzoic acids with N-halosuccinimides.

Halolactonisation reaction first proposed by Bougault<sup>1</sup> has proved to be very useful in determining the structure and stereochemistry of complex molecules. During the course of our investigation on a new approach towards isocoumarins it was found that the cyclisation of acetylenic acids with N-halo compounds leads to  $\gamma$ -methylenebutyrolactones<sup>2</sup>. Earlier we have developed a new method for the synthesis of isocoumarins starting from methyl 2-alkynylbenzoates<sup>3</sup>. As an extension we report herein halolactonisation of 2-alkynylbenzoic acids (I) with N-halo compounds to give isocoumarins(II) in ~ 70% yields (Table 1) (Scheme 1).

This lactonisation opens a new path for the synthesis of isocoumarins. The isocoumarins prepared were fully characterised by analytical and spectral data (IR, UV, PMR) and by comparing these data with those reported in literature. The presence of halogen at the 4-position permits ready elaboration to more complex derivatives.

It is interesting to note that the use of potassium carbonate, triethylamine and pyridine resulted in greatly diminished yields. It was found out by Ranganathan *et al.*<sup>4</sup> that the structure of lactones formed was dependent on the pH of the reaction medium. It was also found that the best yield was obtained with  $\text{CH}_2\text{Cl}_2$  or  $\text{CHCl}_3$  as solvent. Polar solvents resulted in decreased yields than expected.

Further work to throw light on the mechanistic aspect is in progress.

### General procedure for the cyclisation of 2-alkynylbenzoic acids

To a solution of acetylenic acid (I, 0.002 mol) in  $\text{CH}_2\text{Cl}_2$  (25 ml) were added sequentially N-halosuccinimide (0.002 mol),  $\text{NaHCO}_3$  (0.002 mol) and Triton-B (0.4M, 0.5 ml). The reaction mixture



$\text{R} = \text{Ph}$ , Ia;  $p\text{-Br Ph}$ , Ib;

$p\text{-Me Ph}$ , Ic;  $n\text{-Bu}$ , Id

SCHEME 1

Table 1—Yields and Melting Points of Isolated Isocoumarins(II)

Starting acid	N-Halosuccinimide	Isocoumarin(II)	
		Yield (%)	m.p. (°C)
Ia (R = Ph)	NBS	70	130-31
	NIS	68	135
	NCS	69	117
Ib (R = <i>p</i> -Br Ph)	NBS	73	202-4
	NIS	69	167
	NCS	67	184-85
Ic (R = <i>p</i> -Me Ph)	NCS	65	170-71
	NIS	70	174
Id (R = <i>n</i> -butyl)	NCS	68	125-27
	NBS	73	95-96
	NIS	69	102

NBS = N-Bromosuccinimide; NIS = N-iodosuccinimide; and NCS = N-chlorosuccinimide

was stirred for 2 hr, filtered, washed successively with sodium thiosulphate (10%), water, saturated sodium chloride, dried ( $\text{Na}_2\text{SO}_4$ ) and solvent removed. The residue on column chromatography using benzene as the eluant furnished the halosubstituted isocoumarins.

We thank the CSIR, New Delhi for financial assistance to AN.

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## Microbial Transformation of $\alpha$ -Santonin by *Pseudomonas cichorii* S: Identification of Products

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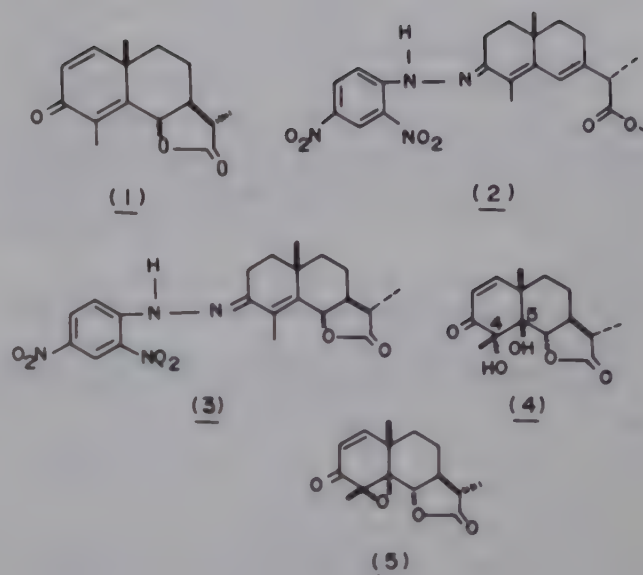
4 $\alpha$ , 5 $\alpha$ -Dihydroxysantonin (4) and ethyl 3-oxoendesma-4, 6-diene-12-oate (2, 4-DNP derivative 3) have been characterised as microbial transformation products of  $\alpha$ -santonin (1) by *Pseudomonas cichorii* S. The assigned structures have been confirmed by their partial chemical synthesis from  $\alpha$ -santonin.

For some time we have been interested in the identification of products obtained during microbial transformation of  $\alpha$ -santonin by microorganisms<sup>1,2</sup>. In continuation of the earlier work from our laboratory, herein we report the isolation and characterisation of products obtained during microbial transformation of  $\alpha$ -santonin<sup>1</sup> by *Pseudomonas cichorii* S in the presence or absence of metabolic inhibitors.

Since the majority of transformation products contain carbonyl group, we considered the possibility of isolating the metabolites as their 2,4-dinitrophenylhydrazone derivatives<sup>3</sup>. Indeed, using 2,4-DNPH as a trapping agent, we could isolate three 2,4-DNP derivatives in pure form.

First of these, m.p. 126°, was identified as acetone 2,4-dinitrophenylhydrazone. The second derivative, m.p. 188°, analysed for C<sub>10</sub>H<sub>10</sub>O<sub>4</sub>N<sub>4</sub> (M<sup>+</sup> 250) and exhibited in its PMR spectrum in CDCl<sub>3</sub> the following signals:  $\delta$  1.96 (3H, d, J = 6.0 Hz), 6.36 (2H, m), 7.80 (1H, d, J = 9.0, Hz), 7.96 (1H, d, J = 9.0 Hz), 8.34 (1H, dd, J = 9.0, 3.0 Hz), 9.16 (1H, d, J = 30 Hz) and 11.08 (1H, s). The spectral data and m.p. permitted the identification of this compound as crotonaldehyde 2,4-dinitrophenylhydrazone.

The third 2,4-DNP derivative, m.p. 150°, was obtained in insufficient amount (5 mg). It analysed for C<sub>23</sub>H<sub>28</sub>O<sub>6</sub>N<sub>4</sub> (M<sup>+</sup> 456) and exhibited in its PMR spectrum in CDCl<sub>3</sub> signals at  $\delta$  1.01 (3H, s), 1.25 (3H, t, J = 6 Hz), 1.36 (3H, d, J = 6 Hz), 2.08 (3H, s), 3.28 (1H, q, J = 6 Hz), 4.15 (2H, q, J = 6 Hz), 6.51 (1H, bs), 8.03 (1H, d, J = 9 Hz), 8.33 (1H, dd, J = 9.0, 3.0 Hz), 9.12 (1H, d, J = 3.0 Hz) and 11.35 (1H, bs). Structure 2 which could be derived for this on spectral evidences was unambiguously confirmed by its partial synthesis



from  $\alpha$ -santonin<sup>1</sup>. Treatment of dihydrosantonin 2,4-DNP (3), m.p. 224° with ethanolic sulphuric acid under refluxing conditions furnished after purification a purple 2,4-DNP derivative in 80% yield identical in all respects with 2.

The use of inhibitors for the accumulation of transformation products in the culture broth is well-known<sup>3-6</sup>. 1,2 Dihydrosantonin, one of the early transformation products of  $\alpha$ -santonin<sup>1</sup> (1) was found to be the major product along with trace quantities of an unidentified polar product when dicyclohexylcarbodiimide (DCC) was used as an inhibitor. On the other hand, five products, all more polar than (1) could be detected in the culture broth when semicarbazide was used as an inhibitor. One of these could be isolated in pure form (m.p. 220°) to which we have assigned structure (4). Its mass spectrum displayed the molecular ion at  $m/z$  280 consistent with molecular formula C<sub>15</sub>H<sub>20</sub>O<sub>5</sub>. The other spectral data for this compound are: UV(EtOH): 226 nm; IR(nujol): 3530, 3478 (hydroxyl), 1775 ( $\nu$ -lactone) and 1678 cm<sup>-1</sup> (conjugated carbonyl), PMR (CDCl<sub>3</sub>):  $\delta$  1.28 (3H, d, J = 6 Hz), 1.39 (3H, s), 1.56 (3H, s), 4.02 (1H, s, exchangeable with D<sub>2</sub>O), 4.16 (1H, s, exchangeable with D<sub>2</sub>O), 4.20 (1H, d, J = 12 Hz), 6.02 (1H, d, J = 10 Hz) and 6.38 (1H, d, J = 10 Hz). These spectral data clearly showed that this transformation product is 4,5-dihydroxysantonin (4) (excluding stereochemistry at C-4 and C-5). Although it is previously suggested<sup>7</sup> that the 4,5-dihydroxysantonin, m.p. 261° obtained by KMnO<sub>4</sub> oxidation of 1 should be 4 $\alpha$ , 5 $\alpha$ -dihydroxysantonin (4) we could not find any report confirming this assignment. There are also no reports on the preparation of

4 $\alpha$ , 5 $\beta$  or 4 $\beta$ , 5 $\alpha$  -diols from  $\alpha$  -santonin. The preparation of these diols was therefore, essential for determining the stereochemistry of the newly created hydroxyl groups at C-4 and C-5. Santonin  $\alpha$  -epoxide<sup>7</sup> (5) failed to undergo oxirane ring cleavage under a variety of conditions. However, oxidation of santonin with KMnO<sub>4</sub>/pyridine led to 4 $\alpha$ , 5 $\alpha$ -dihydroxysantonin, m.p. 220° identical in all respects with the microbial transformation product, which is therefore 4. It should be noted, however, that the m.p. of *cis*-diol (4) is 220° and not 261° (ref. 87) as previously reported.

Identification of other transformation products is in progress.

We thank Dr A F Thomas for spectral data and the

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## Isotirumalin, a New Prenylated Dihydroflavonol from *Rhynchosia cyanosperma* (Benth)

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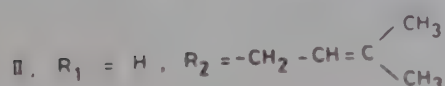
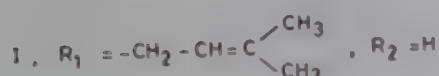
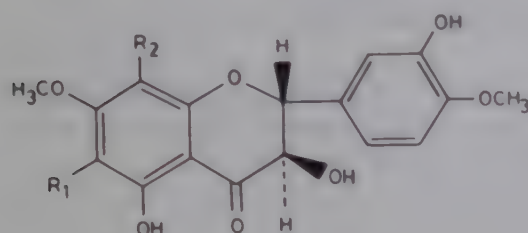
Isotirumalin, a new prenylated dihydroflavonol, isolated from the leaves of *Rhynchosia cyanosperma* (Benth), has been characterised as 6-C-prenyltaxifolin-7,4'-dimethyl ether (I) on the basis of spectral and chemical studies.

In continuation of our work<sup>1</sup> on the phenolic constituents of *Rhynchosia cyanosperma* Benth (fam: Leguminosae), we now report the isolation and structure elucidation of isotirumalin (I), a new prenylated dihydroflavonol isomeric with tirumalin<sup>1</sup> (II) from the benzene extract of the leaves of this plant.

The air-dried and powdered leaves (2 kg) of *R. cyanosperma* procured from Tirumala Hills, Tirupati, Andhra Pradesh were successively extracted with petrol (60-80°) and benzene. The benzene extract was concentrated under reduced pressure and the residue left behind was treated with hot petrol (60-80°). The petrol soluble part on concentration afforded isotirumalin (I) as a pale yellow solid which was crystallised from MeOH as pale yellow solid which was crystallised from MeOH as pale yellow needles (15 mg), m.p. 190-91°,  $[\alpha]_D^{25} + 25.35^\circ$  (c, 0.7, MeOH). It analysed for C<sub>22</sub>H<sub>24</sub>O<sub>7</sub> (400.40) (Found: C, 65.9; H, 6.4. C<sub>22</sub>H<sub>24</sub>O<sub>7</sub> requires C, 66.0; H, 6.0%). It gave a violet colour with alcoholic FeCl<sub>3</sub>, a dark blue colour with Gibb's reagent, and a pink colour with Mg-HCl and Zn-HCl. Its

IR spectrum (KBr) exhibited strong absorptions at 3420 (-OH) 1630 (chelated C=O) and 1370 cm<sup>-1</sup> (gem-dimethyl). Its UV spectrum in MeOH ( $\lambda_{\max}$ : 290, 325 nm) suggested a flavanone or dihydroflavonol structure. A bathochromic shift of 24 nm with aluminium chloride showed the presence of a free hydroxyl at 5-position.

The 60MHz PMR spectrum of I in DMSO-*d*<sub>6</sub> exhibited the typical AB system due to C-2 and C-3 methine protons of dihydroflavonols<sup>2</sup> at  $\delta$  5.10 (*d*, *J* = 11 Hz) and 4.52 (*d*, *J* = 11 Hz) respectively. The presence of a C-linked prenyl residue<sup>3,4</sup> was inferred from the signals at  $\delta$  5.12 (*t*, *J* = 7 Hz, 1H,  $\beta$ -CH=), 3.08 (*d*, *J* = 7 Hz, 2H,  $\alpha$ -CH<sub>2</sub>) and 1.54, 1.57 (2  $\times$  s, 2  $\times$  3H,  $\gamma$ -Me<sub>2</sub>). A broad three-proton singlet at  $\delta$  6.94 was assigned to 2', 5' and 6' protons of ring-B<sup>1-5</sup>. Two broad signals at  $\delta$  11.81 and 9-.10 were assigned to chelated hydroxyl at C-5 (supported by strong ferric colour) and non-chelated hydroxyl respectively. The presence of three hydroxyl groups in I was evidenced by the formation of a triacetate (m.p. 95-96°, M<sup>+</sup> 526). Two three-proton singlets at  $\delta$  3.82 and 3.80 could be assigned to two methoxyl groups. That the former signal was due to CH<sub>3</sub>O at 7-position was supported by the fact that there was no bathochromic shift of the UV absorption maximum with sodium acetate. Since the signal due to H-2' in the triacetate of I appeared at a lower field ( $\delta$  7.15) than H-5' proton signal ( $\delta$  7.02), placed non-chelated hydroxyl at 3'-position<sup>6</sup> and the second methoxyl at C-4'. The A-ring aromatic proton appearing as a singlet at  $\delta$  5.99 was assigned to H-8 proton on the basis of comparison with the chemical shift value of  $\delta$  6.23 exhibited by H-6 proton of tirumalin (II). Thus the prenyl residue in isotirumalin (I) was shown to be located at C-6 which was also supported by a positive Gibb's test. A *trans*-orientation of the C-ring methine protons was inferred from the large *J* value (11 Hz) which was typical of diaxial coupling<sup>2</sup>. Positive optical rotation of I indicates 2*R*, 3*R*-configuration and hence I was characterised as (+)-(2*R*, 3*R*)-6C-prenyltaxifolin-7,4'-dimethyl ether (I). The structure (I) was further supported by its mass spectrum which showed a molecular ion peak at *m/z* 400, an [A<sub>1</sub> + H]<sup>+</sup> fragment at *m/z* 235 consistent with an A-ring with one hydroxyl, one methoxyl and a prenyl residue, and a [B<sub>3</sub>]<sup>+</sup> fragment at *m/z* 166 consistent with the presence of one hydroxyl and one methoxyl in the B-ring.



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## Studies in Medicinal Plants: Part XVI<sup>1</sup>—A New Xanthone from *Hypericum mysorens* Heyne

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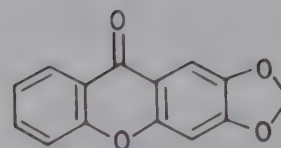
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2,3-Methylenedioxyxanthone, a new xanthone, has been isolated from *Hypericum mysorens* Heyne. Its structure has been assigned on the basis of spectral data and confirmed by synthesis. Seven other known xanthones have also been isolated from the anti-fungal fraction of the plant.

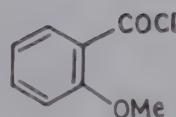
In continuation of our work<sup>1-5</sup> on the chemistry of *Hypericum mysorens* Heyne (Hypericaceae), we now report the isolation, characterization and synthesis of a new compound, 2,3-methylenedioxyxanthone (I), along with seven known xanthones, 2-methoxyxanthone (V) (m.p. 130°), 1,2-dimethoxyxanthone (VI) (m.p. 129°), 2,3-dimethoxyxanthone (VII) (m.p. 154-55°), 2-hydroxyxanthone (VIII) (m.p. 230°), 1,5-dihydroxy-3-methoxyxanthone (IX) (m.p. 270°), 3-hydroxy-2-methoxyxanthone (X) (m.p. 175°) and 6,7-dimethoxy-1-hydroxyxanthone (XI) (m.p. 186°). All these xanthones were characterized on the basis of data already reported<sup>6-11</sup>; compounds IX and X are reported from this plant for the first time.

The ethanol extract (100 g) of aerial parts of *H. mysorens* was fractionated into hexane, ethyl acetate and *n*-butanol fractions. The ethyl acetate fraction (22 g) was subjected to column chromatography over silica gel. Elution with 10% ethyl acetate-benzene afforded a mixture of xanthones which were purified by repeated chromatography.

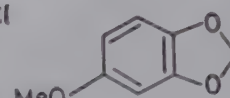
The compound (I) analysed for C<sub>14</sub>H<sub>8</sub>O<sub>4</sub> (M<sup>+</sup>, 240) and crystallised from ethyl acetate-hexane as colourless needles, m.p. 192°. Its UV spectrum in methanol (239, 270, 304 and 348 nm) and IR spectrum in KBr (1640, 1480 and 1320 cm<sup>-1</sup>) were consistent with those reported for polyoxygenated xanthones<sup>12</sup>. The PMR spectrum of I in CDCl<sub>3</sub> displayed signals at  $\delta$  6.10 (s, 2H, O-CH<sub>2</sub>-O), 6.90 (s, C<sub>4</sub>-H), 7.50 (s, 1H, C<sub>1</sub>-H), 7.35-7.56 (m, 3H, C<sub>5</sub>-, C<sub>6</sub>- and C<sub>7</sub>-H), 8.30 (dd,



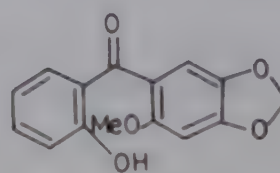
( I )



( II )



( III )



( IV )

1H, C<sub>8</sub>-H). The orientation of methylenedioxy group (two-proton singlet at  $\delta$  6.10) at 2,3-positions of xanthone nucleus was confirmed by the appearance of two singlets at 6.90 and 7.50 assignable to C-4 and C-1 protons respectively. The C-8 proton, *perito* the carbonyl appeared characteristically at  $\delta$  8.30, a multiplet ~ 7.35-7.65 for three protons was assigned for C-5, C-6 and C-7 protons. The chemical shifts of all the carbons have been assigned by <sup>13</sup>C NMR spectral data:  $\delta$  180 (C-9), 156 (C-4b), 154 (C-4a), 134 (C-6), 126 (C-8), 124 (C-7), 117 (C-5), 112 (C-8a), 111 (C-9a), 103 (C-2 and C-3), 102 (C-1 and C-4) and 98 (C-10). The mass spectral data showed base peak at 240 and other peaks at *m/z* 241, 239 and 126.

The structure I was confirmed through its synthesis by base-catalyzed cyclization of IV, which in turn was obtained by Friedel-Crafts acylation<sup>6</sup> of 2-methoxybenzoyl chloride (II) with O-methylsesamol (III).

### 2'-Hydroxy-2-methoxy-4,5-methylenedioxybenzophenone (IV)

To a mixture of 2-methoxybenzoyl chloride (II, 1 g), O-methylsesamol (III, 1.7 g) in dry ether (40 ml) was added anhydrous AlCl<sub>3</sub> (1.7 g). The red-brown two-phase system was stirred for 21 hr, ether evaporated off and the residue poured into HCl (10%, 15 ml) and ice. The aqueous layer was extracted with benzene (3 x 80 ml). The organic layer was washed with water, dried (Na<sub>2</sub>SO<sub>4</sub>), concentrated to an oily residue (2.0 g) which was purified by column chromatography on silica gel to afford IV (1.8 g) m.p. 95-97°; UV (MeOH): 242, 282 and 356 nm; IR (KBr): 1620, 1495, 1420,

1350, 1250, 1200, 1050 and 950  $\text{cm}^{-1}$ ; PMR ( $\text{CDCl}_3$ ):  $\delta$  3.77 (s, 3H, OMe), 5.90 (s, 2H, O- $\text{CH}_2$ -O), 6.46 (s, 1H,  $\text{C}_6$ -H), 6.60 (s, 1H,  $\text{C}_3$ -H), 7.0 (m, 2H,  $\text{C}_4$ -H and  $\text{C}_5$ -H) and 7.80 (dd, 1H,  $\text{C}_6$ -H); MS ( $m/z$ ): 272 ( $\text{M}^+$ ), 273, 241 (base peak), 163, 135, 106, 91 and 77.

### 2,3-Methylenedioxyxanthone (I)

Compound (IV, 1g) was refluxed (6hr) with a solution of sodium hydroxide (1.2g) in methanol (6ml) and water (4ml). The mixture was left overnight, the crystalline precipitate was filtered, washed with water and recrystallised to afford I (80 mg), m.p. and m.m.p. 192°. Spectral data (UV, IR and PMR) of synthetic I were superimposable with those of natural I.

One of us (SB) thanks the CSIR, New Delhi for the award of a junior research fellowship.

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## Isorhamnetin 3-O-Rutinoside from Leaves of *Azima tetracantha* Lam.

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The title glycoside has been isolated from the leaves of *Azima tetracantha* Lam. The isolation of this relatively rare glycoside assumes significance since it has earlier been located in only three other plant sources, viz. *Narcissus tazetta*, *Lilium auratum* and *Bupleurum rotundifolium*.

*Azima tetracantha* Lam. (Monetia L'Heritier) (syn. *A. lamarck*, *Monetia tetracantha*) is an evergreen ornamental shrub belonging to the family Salvadoraaceae and growing to about 3 feet in tropical conditions<sup>1-3</sup>. The leaves, roots and a decoction of the juice obtained from the root bark find use in the indigenous system of medicine<sup>2</sup>. Friedelin, glutinol, lupeol and  $\beta$ -sitosterol have been isolated<sup>4</sup> from the leaves and roots of *A. tetracantha* collected in Andhra Pradesh and the yield of terpenoids from the roots has been found to be much lower than that from leaves. Herein we report the isolation and characterisation of a relatively rare flavanol bioside, isorhamnetin 3-O-rutinoside from the leaves of *A. tetracantha*.

Shade-dried leaves of *A. tetracantha*, collected from Viralimalai about 30 km south of Tiruchirapalli during early summer were extracted with 80% ethyl alcohol under reflux and the concentrate worked up for flavonoid constituents by standard procedure<sup>5,6</sup>. The residue from the petrol fraction exhibited in the UV (petrol) maximum absorptions at 412, 431, 444(sh), 506, 541, 564, 613 and 672 nm indicating the presence of chlorophyll. The EtOAc concentrate afforded a compound as pale yellow needles (MeOH), m.p. 182-84° (lit. 174°), yield 0.28%; UV (MeOH): 256, 268(sh), 354; + NaOMe 256, 413; + AlCl<sub>3</sub> 256, 405 with and without HCl; + NaOAc 270, 380; + H<sub>3</sub>BO<sub>3</sub> 256, 354 nm. It was soluble in MeOH and DMSO and gave greenish-brown colouration with alc. FeCl<sub>3</sub>. The compound appeared deep purple under UV changing to yellow on fuming with NH<sub>3</sub> and formed a diacetate, m.p. 200-202° (lit. 202-204°). On hydrolysis (2N H<sub>2</sub>SO<sub>4</sub>, 2 hr, 100°) it afforded isorhamnetin, glucose and rhamnose (1:1:1). When cleaved with H<sub>2</sub>O<sub>2</sub> in the presence of ammonia<sup>6</sup>, it yielded rutinose. The 90

MHz PMR spectrum of the glycoside (DMSO-TMS) displayed the following signals:  $\delta$  6.2(H-6), 6.4(H-8), 8.0(H-2'), 6.9(H-5'), 7.4(H-6'), 3.8(3'-OCH<sub>3</sub>), 4.4(H-1, rhamnose) and 1.2-1.0 (*m*, methyl protons of rhamnose). The other sugar protons were located in the region  $\delta$  3.7 and 2.5. The 22.5 MHz <sup>13</sup>CNMR spectrum of the glycoside (DMSO-TMS) recorded under proton noise-decoupled conditions revealed the signals that could be assigned to various carbons as follows:  $\delta$  156.425 (C-2, C-9), 133.014 (C-3), 177-235 (C-4), 161.108 (C-5), 98.873 (C-6), 164.687 (C-7), 93.865 (C-8), 103.685 (C-10), 120.983 (C-1'), 115.131 (C-2', C-5'), 149.467 (C-3'), 146.931 (C-4'), 130.868 (C-6'), 100.043 (C-1'', C-1'''), 76.762 (C-2'', C-3'', C-5''), 73.056 (C-4''), 71.885 (C-2'''), 70.584 (C-3'''), 68.243 (C-6'', C-5'''), 73.576 (C-4'''), 17.845 (C-6''') and 55.887 (C-3'-OCH<sub>3</sub>). The signals at 100.043 and 68.243 due to C-1'' and C-6'' show that rutinosyl moiety is located at C-3 of the flavonol moiety. The glycoside has therefore been characterised as isorhamnetin 3-O-rutinoside (=narcissin). The glycoside has so far been isolated from only three other sources, viz. *Narcissus tazetta*<sup>7</sup>, *Lilium auratum*<sup>8</sup> and *Bupleurum rotundifolium*<sup>9</sup>. The present report of isolation of this flavonol glycoside of rare occurrence can therefore be considered significant.

The authors thank Prof. Michael S Tempesta, Director, Analytical Service Centre, University of Missouri Columbia, USA for the NMR spectra and Dr K V Krishnamurthi and K Sigamani of our Botany Department for collection and identification of the plant. One of the authors (UVW) is grateful to the UGC, New Delhi for the award of a teacher fellowship under the F.I.P. scheme.

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## Lignans from Leaves of *Piper nigrum* Linn.

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From the petrol and chloroform extracts of the leaves of *Piper nigrum* Linn. two isomeric lignans (–)-3,4-dimethoxy-3,4-desmethylenedioxycubebin and (–)-3',4'-dimethoxy-3',4'-desmethylenedioxycubebin have been isolated in pure form along with (–)-cubebin.

*Piper nigrum* Linn. berries (black pepper) are widely used in indigenous system of medicine<sup>1</sup>. More than 100 terpene constituents have been reported from the essential oil<sup>2</sup> of the berries. Several alkaloids<sup>3</sup> have been isolated as non-volatile constituents. Piperine,  $\beta$ -sitosterol, hentriacontane, hentriacontanone-16 and hentriacontanol-16 are reported in the stems of *P. nigrum*<sup>3</sup>. Three dibenzylbutyrolactol lignans, (–)-cubebin and (–)-cubebinin<sup>4</sup> from *P. cubeba* and (–)-clusin<sup>5</sup> from *P. clusii* are so far reported from the genus *Piper*. Herein, we report the isolation and identification of three dibenzylbutyrolactol lignans from *P. nigrum* leaves. We also took this opportunity to completely characterise the two isomeric lignans.

The petroleum ether and the chloroform extracts of dried powdered *P. nigrum* leaves on repeated column chromatography and preparative TLC gave three crystalline compounds A-C. Compound-A was identified as (–)-cubebin by its superimposable IR, PMR and mass spectra with that of an authentic sample.

The 500 MHz PMR spectra of compounds B and C were very similar and indicated their identity as dibenzylbutyrolactol lignans. The *trans*-stereochemistry at 8 and 8' positions was established by the characteristic PMR spectra<sup>5</sup> (60 MHz;  $\delta$  2.50, *m*, 4H, benzylic protons and 2.85, *m*, 2H, methine protons) of the lactones obtained by oxidation with  $\text{CrO}_3/\text{H}_2\text{SO}_4$  in acetone<sup>7</sup>. The mass spectrum of B showed base peak at *m/z* 151 as observed by Rucker *et al.*<sup>6</sup> and established its identity as 3,4-dimethoxy-3,4-desmethylenedioxycubebin. Compound-C showed base peak at *m/z* 135, thus establishing<sup>6</sup> its structure as 3',4'-dimethoxy-3',4'-desmethylenedioxycubebin. These two lignans were earlier isolated as the corresponding lactones from *Aristolochia triangularis* by Rucker *et al.*<sup>7</sup>.

The methanol soluble portion of the petroleum ether extract of the berries also showed the presence of these three lignans by co-TLC.

## Extraction and separation of compounds

The leaves of *P. nigrum*, obtained from the local gardens, were shade dried, powdered (625 g) and extracted successively with petroleum ether (60-70°) and chloroform in a Soxhlet apparatus for 40 hr and 30 hr respectively. The methanol soluble fraction of the petroleum ether extract (20 g) and the chloroform extract (14 g) were separately subjected to column chromatography (silica gel, 250 g and 200 g respectively). The mixed residue (23 g) from 9:1 chloroform-methanol eluates was rechromatographed over silica gel (175 g). A fraction from chloroform-ethyl acetate (95:5) eluate showed the presence of two closely moving spots [solvent system benzene-ethyl acetate 9:1 (UV)]. The residue from this fraction (2 g) was subjected to preparative TLC (UV); upper band gave the compound-A (3.8 mg), which recrystallised from benzene-hexane.

The extract from the lower band on fractional crystallisation followed by further recrystallisations from benzene-hexane gave compound B (11.5 mg) and C (5 mg).

(–)-3,4-Dimethoxy-3,4-desmethylenedioxycubebin (B): white needles, m.p. 86-87° (lit.<sup>6</sup> 89-91°),  $[\alpha]_D^{25} - 52.86$  ( $\text{CHCl}_3$ ; *c* 0.35) (Found:  $\text{M}^+$ , 372.1575.  $\text{C}_{21}\text{H}_{24}\text{O}_6$  requires 372.1574); MS *m/z* (rel. int.): 372 ( $\text{M}^+$ , 33.7), 203 (19.1), 177 (73.3), 152 (82), 151 (100), 145 (13.9), 135 (50.4), 123 (11.7), 121 (19.1), 81 (24.9).

(–)-3',4'-Dimethoxy-3',4'-desmethylenedioxycubebin (C): white globules, m.p. 66°,  $[\alpha]_D^{25} - 15.88$  ( $\text{CHCl}_3$ ; *c* 0.17); UV (MeOH): 236 and 286 nm; IR (KBr): 3365 (OH), 2940, 1605, 1530, 1500, 940 and 820  $\text{cm}^{-1}$ ; PMR (500 MHz,  $\text{CDCl}_3/\text{TMS}$ ):  $\delta$  2.0-2.9 (6H, *m*, 4-benzylic and 2-methine protons), 3.82 and 3.85 (6H, *s*, Ar-OCH<sub>3</sub>), 3.59, 4.01 and 4.10 (2H, triplets, *J* = 8 Hz each, methylene protons of furanol ring), 5.23 (1H, *s*, hemiacetal proton), 5.92 (2H, *s*, OCH<sub>2</sub>O), 6.4-6.9 (6H, *s*, ArH); (Found:  $\text{M}^+$ , 372.1576.  $\text{C}_{21}\text{H}_{24}\text{O}_6$  requires 372.1574); MS: *m/z* (rel. int.): 372 ( $\text{M}^+$ , 11.6), 203 (5.4), 177 (25.8), 152 (46.9), 151 (77.7), 145 (4.9), 135 (100), 123 (75), 121 (11), 81 (7.7) (Found: C, 67.5; H, 6.4.  $\text{C}_{21}\text{H}_{24}\text{O}_6$  requires C, 67.7; H, 6.5%).

We thank Dr N B Mulchandani, Bio-Organic Division, BARC, Bombay for an authentic sample of (–)-cubebin. We are also thankful to Dr M M Dhingra, TIFR, Bombay for the 500 MHz PMR spectra of compounds B and C.

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## Glucopyranosides Derived from Allopurinol & Their Xanthine Oxidase Inhibitory Activity

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N<sup>1</sup>,N<sup>5</sup>-Bis( $\alpha$ - and  $\beta$ -D-glucopyranosides) (VIa and VIIa), and N<sup>1</sup>- $\alpha$ -, N<sup>2</sup>- $\beta$ - and N<sup>5</sup>- $\beta$ -D-glucopyranosides (VIIIa, IXa and Xa) of allopurinol have been prepared by glycosidation of allopurinol via the corresponding bis-trimethylsilyl intermediate and penta-O-acetyl- $\alpha$ -D-glucopyranose in the presence of tin tetrachloride as catalyst, and tested for their xanthine oxidase inhibitory activity *in vivo*. The structure of these products have been assigned on the basis of their UV, PMR and <sup>13</sup>C NMR spectral data.

Allopurinol, 1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one (I), synthesized by Robins<sup>1a</sup> and Durey<sup>1b</sup>, has acquired pharmacological importance mainly due to its resemblance with hypoxanthine both structurally as well as biologically, which eventually results in the inhibition of specific enzyme in purine and pyrimidine metabolism. Thus, allopurinol (I) is a potent inhibitor of xanthine oxidase and for this reason it is widely used in the treatment of gout<sup>2</sup>. The N<sup>1</sup>-riboside (II) has substantial antiparasitic activity<sup>3</sup> and the 1-ribotide (III) exhibits antiviral and antitumor activities<sup>4,5</sup>.

In continuation of our work on the preparation of glycosides of the natural products<sup>6</sup>, we report herein the preparation and xanthine oxidase inhibitory activity of various glucopyranosides of I.

N-Glycosidation of silylated pyrimidines with fully acylated sugars<sup>7</sup> has been found to be a suitable procedure for preparing purine nucleosides from silylated purines<sup>8</sup>. Application of this procedure to a silylated allopurinol (IV) appeared to be analogous to the glycosidation of bis(trimethylsilyl)hypoxanthine<sup>9</sup>, and was expected to occur in the pyrazole as well as pyrimidine moieties of IV.

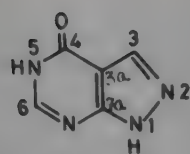
The required 1,4-bis(trimethylsilyl)allopurinol (IV) was readily obtained in crystalline form by refluxing I in hexamethyldisilazane in the presence of a catalytic amount of (NH<sub>4</sub>)<sub>2</sub>SO<sub>4</sub>. It reacted with 1,2,3,4,6-penta-O-acetyl- $\alpha$ -D-glucopyranose (V) in the presence of freshly distilled stannic chloride in dry dichloroethane at 60° to give a mixture of five compounds which were separated by column chromatography on silica gel. The first mobile

component obtained was identified as 1,5-dihydro-1,5-bis(2,3,4,6-tetra-O-acetyl- $\alpha$ -D-glucopyranosyl)-4H-pyrazolo[3,4-d]pyrimidin-4-one (VIa) on the basis of mass, PMR, <sup>13</sup>C NMR and UV spectral data. The next eluate afforded a compound isomeric to VIa and was identified as 1,5-dihydro-1,5-bis(2,3,4,6-tetra-O-acetyl- $\beta$ -D-glucopyranosyl)-4H-pyrazolo[3,4-d]pyrimidin-4-one (VIIa) on the basis of the downfield <sup>13</sup>C NMR signal for the two anomeric carbons centred at  $\delta$  88.5 in VIIa as compared to <sup>13</sup>C NMR signals for the two anomeric carbons centred at  $\delta$  81.5 and 78.0 in VIa. The UV spectra of the bis-glucosides VIb and VIIb closely resembled that of 1,5-dimethylallopurinol<sup>10</sup>, and remained unaltered between pH 7 and 11 (Table 1) due to the absence of dissociable protons.

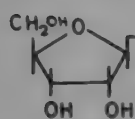
The next three eluates yielded fractions C (VIIa), D (IXa) and E (Xa) which were found to contain isomeric monoglucoside derivatives of allopurinol. The three compounds had the same molecular formula. The identification of compound VIIIa as 1,5-dihydro-1-(2,3,4,6-tetra-O-acetyl- $\alpha$ -D-glucopyranosyl)-4H-pyrazolo[3,4-d]pyrimidin-4-one was supported by its UV, PMR and <sup>13</sup>C NMR spectral data. The structural assignment of IXb as allopurinol-2- $\alpha$ -D-glucoside was based on the bathochromic shift of UV maxima at pH 7 and 11 as compared with the N<sup>1</sup>-isomer (VIIIb) indicating the orthoquinonoid distribution of electron and also on the basis of PMR and <sup>13</sup>C NMR spectra. The  $\beta$ -configuration for the N<sup>5</sup>-glucosyl derivative (Xa) was indicated by a PMR doublet due to anomeric hydrogen at 632 ( $J = 9$  Hz). The UV spectra of the neutral species of N<sup>1</sup>-(VIIIb) and N<sup>5</sup>-(Xb) derivatives were practically identical with that of allopurinol. Dissociation of the 5-NH in the pyrimidine moiety of VIIIb and IXb at pH 11 led to a marked bathochromic shift, whereas ionization of NH proton in the pyrazole moiety as in Xb brought about minor or no change. The <sup>13</sup>C NMR spectrum of VIIIa exhibited signals at  $\delta$  82.5 which supported the  $\alpha$ -configuration of the anomeric carbon of glucose whereas the <sup>13</sup>C NMR spectrum of IXa displayed a signal due to anomeric carbon of glucose at  $\delta$  87.0 which supported the  $\beta$ -configuration of the glucose molecule.

### Biological activity

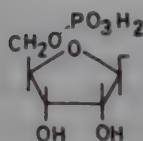
Xanthine oxidase activity was determined spectrophotometrically by estimating uric acid at 290



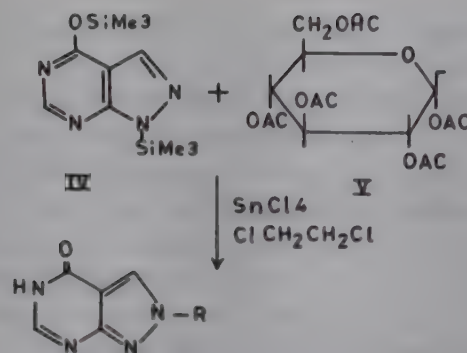
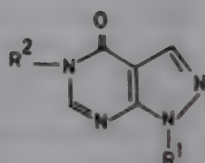
I, R = H



II, R



III, R

IXa; R = 2-(2,3,4,6-TETRA-O-ACETYL  $\beta$ -D-GLUCOPYRANOSYL)IXb; R = 2-( $\beta$ -D-GLUCOPYRANOSYL)

VIa; R<sup>1</sup> = R<sup>2</sup> = 1,5-BIS-(2,3,4,6-TETRA-O-ACETYL- $\alpha$ -D-GLUCOPYRANOSYL)

VIb; R<sup>1</sup> = R<sup>2</sup> = 1,5-BIS-( $\alpha$ -D-GLUCOPYRANOSYL)

VIIa; R<sup>1</sup> = R<sup>2</sup> = 1,5-BIS-(2,3,4,6-TETRA-O-ACETYL- $\beta$ -D-GLUCOPYRANOSYL)

VIIb; R<sup>1</sup> = R<sup>2</sup> = 1,5-BIS-( $\beta$ -D-GLUCOPYRANOSYL)

VIIIa; R<sup>2</sup> = H, R<sup>1</sup> = 1-(2,3,4,6-TETRA-O-ACETYL- $\alpha$ -D-GLUCOPYRANOSYL)

VIIIb; R<sup>2</sup> = H, R<sup>1</sup> = 1-( $\alpha$ -D-GLUCOPYRANOSYL)

IXa; R<sup>1</sup> = H, R<sup>2</sup> = 5-(2,3,4,6-TETRA-O-ACETYL  $\beta$ -D-GLUCOPYRANOSYL)

IXb; R<sup>1</sup> = H, R<sup>2</sup> = 5-( $\beta$ -D-GLUCOPYRANOSYL)

Table 1—Physical Data of Allopurinol Glucoside

Site of glycosidation	Compd	[ $\alpha$ ] <sub>D</sub> <sup>20</sup> (c, solvent <sup>a</sup> )	UV (MeOH) (in nm) at				PMR ( $\delta$ ppm) <sup>†</sup>			
			pH 7		pH 11		3H <sup>†</sup>	6H <sup>†</sup>	1'-H	1''-H
			max	min	max	min				
N <sup>1</sup> ,N <sup>5</sup> - $\alpha$	VIa	-4° (1.0, A)	250	234	—	—	8.18	8.24	6.32 (d, J = 7.0)	6.08 (d, J = 5.0)
	VIb	-16° (1.0, M)	254	240	250	234	—	—	—	—
N <sup>1</sup> ,N <sup>5</sup> - $\beta$	VIIa	-24° (1.0, A)	258	238	—	—	8.22	8.55	6.22 (d, J = 10)	5.80 (d, J = 10)
	VIIb	-50° (0.2, M)	258	240	258	240	—	—	—	—
N <sup>1</sup> - $\alpha$	VIIIa	-4° (1.0, A)	250	230	—	—	8.04	8.18	6.08 (d, J = 2.5)	—
	VIIIb	+20° (0.1, M)	256	236	266	236	—	—	—	—
N <sup>2</sup> - $\beta$	IXa	-22° (0.5, A)	264	236	—	—	8.00	8.82	6.13 (d, J = 10)	—
	IXb	+40° (0.5, M)	260	238	286	256	—	—	—	—
N <sup>5</sup> - $\beta$	Xa	-45° (0.2, A)	250	232	—	—	8.18	8.32	6.32 (d, J = 9)	—
	Xb	+3.3° (0.3, M)	252	234	250	232	—	—	—	—

<sup>a</sup>A = acetone, M = methanol.

<sup>†</sup>Assignments of 3H and 6H are tentative and may have to be interchanged.

<sup>‡</sup>PMR spectra were in CDCl<sub>3</sub> except that of IXa which was recorded in DMSO-d<sub>6</sub>; J values in Hz.

nm<sup>11</sup>. The reaction mixture in a total volume of 2.0 ml contained 100  $\mu$ moles tris-HCl (pH 8.0), 0.6  $\mu$ moles xanthine as substrate and a suitable aliquot of post mitochondrial supernatant from rat liver. The reaction was initiated by the addition of the substrate after a preincubation for 5 min at 37° and quenched by the addition of 1.0 ml perchloric acid (10%, w/v) after an incubation for 30 min at 37°. The uric acid formed was estimated at 290 nm. The results are given in Table 2.

Among the compounds tested Xb was found to be relatively more active (62% inhibition at  $5 \times 10^{-5}$  M) than other compounds. However, its inhibitory effect was less than that of allopurinol (76% inhibition at  $1 \times 10^{-6}$  M). It is understandable that compound Xb might show better pharmacological effect than allopurinol in view of the fact that the latter is lipophylic and its high doses are required for therapeutic effects. However, allopurinol glucosides are water soluble and therefore better absorption from stomach is expected. This is a preliminary report and studies are in progress on these lines.

An attempt was also made to determine the structure activity relationship. Compound VIIb did not show any inhibition even at  $1 \times 10^{-3}$  M, concentration whereas Xb offered maximum inhibitory activity. This indicates that the presence of  $\beta$ -D-glucose at position N-1 in addition to N-5 renders the compound ineffective. Likewise, VIb and VIIb show that the presence of  $\alpha$ -D-glucose at position N-1 in addition to N-5 decreases the xanthine oxidase inhibitory activity. It has also been observed that in the case N-1 and N-5, if both are occupied by glucose (VIb and VIIb),  $\alpha$ -glucoside (VIb) is active. Thus, position as well as  $\alpha$ - or  $\beta$ -linkage of the sugar determine the biological activity of the compound.

#### 1-Trimethylsilyl-4-trimethylsilyloxy-1H-pyrazolo[3,4-d]pyrimidine (IV)

A mixture of I (4.5 g, 32 mmol), hexamethyldisilazane (16.0 g, 0.1 mol) and a trace of ammonium sulphate (10 mg) was refluxed under anhydrous condition until a clear solution was obtained (10 h). On cooling to room temperature partial crystallization took place. Removal of the excess hexamethyldisilazane *in vacuo* gave IV as colourless crystals, m.p. 86.

#### Tin tetrachloride-catalysed glycosidation of IV with 1,2,3,4,6-penta-O-acetyl- $\alpha$ -D-glucopyranose (V): Formation of acetylated allopurinol glucosides

To a solution of IV (8.6 g, 32 mmol) and V (10.5 g, 28 mmol) in 1,2-dichloromethane (100

Table 2—Xanthine Oxidase Inhibitory Activity of VIb, VIIIb and Xb

Per cent inhibition of xanthine oxidase activity* of				
Concentration (final)	VIb†	VIIIb†	Xb†	Allopurinol‡
$1 \times 10^{-6}$ M	—	—	—	76.00
$1 \times 10^{-5}$ M	—	6.20	22.66	94.00
$5 \times 10^{-5}$ M	—	25.00	61.38	100.00
$1 \times 10^{-4}$ M	10.37	47.70	88.00	—
$5 \times 10^{-4}$ M	17.48	—	100.00	—
$1 \times 10^{-3}$ M	78.00	—	—	—

\*Values reported are the mean of three determinations in duplicate. Control experiment represented 0.064 units xanthine oxidase activity. One unit of xanthine oxidase activity will convert 1  $\mu$ mol of xanthine to uric acid/mg protein/30 min under the assay conditions.

†Dissolved in distilled water.

‡Dissolved in DMSO and added to 0.1 ml aliquot to the reaction mixture 0.1 ml amount of DMSO is devoid of any inhibitory effect on xanthine oxidase activity.

ml) were added molecular sieve 4Å (5g) and tin tetrachloride (6.0 ml, 50 mmol) and the mixture was stirred at 60° for 6 hr under anhydrous condition. The molecular sieve was removed and the solution after dilution with 1,2-dichloroethane (300 ml) was extracted with aq. NaHCO<sub>3</sub> solution and washed with water. Drying of the organic layer over Na<sub>2</sub>SO<sub>4</sub> and evaporation to dryness left a yellowish foam (5g) which contained a number of compounds (TCL). The whole mixture was subjected to column chromatography on silica gel to give the fractions of the pure compounds. Evaporation of eluates gave the following compounds.

**Fraction A**—It crystallized from ethanol giving 1,5-dihydro-1,5-bis(2,3,4,6-tetra-O-acetyl- $\alpha$ -D-glucopyranosyl)-4H-pyrazolo[3,4-d]pyrimidin-4-one (VIa), yield 0.8 g, m.p. 232–35° (Found: C, 49.9; H, 6.4; N, 6.9. C<sub>33</sub>H<sub>40</sub>O<sub>19</sub>N<sub>4</sub> requires C, 49.7; H, 5.0; N, 7.0%); CMR(CDCl<sub>3</sub>):  $\delta$  61.5 (2  $\times$  C-6'), 67.5 (C-4'), 69.0 (C-4'), 71.0 (C-2'), 72.0 (C-2'), 73.0 (C-5'), 74.0 (C-5'), 74.5 (C-3'), 78.0 (C-1' and C-3'), 81.5 (C-1'), 104.1 (C-3a), 136.1 (C-3), 146.5 (C-6), 151.5 (C-7a) and 155.0 (C-4).

**Fraction B**—It crystallized from ethanol giving 1,5-dihydro-1,5-bis(2,3,4,6-tetra-O-acetyl- $\beta$ -D-glucopyranosyl)-4H-pyrazolo[3,4-d]pyrimidin-4-one (VIIa), yield 0.5 g, m.p. 256–58° (Found: C, 49.6; H, 5.0; N, 7.0. C<sub>33</sub>H<sub>40</sub>O<sub>19</sub>N<sub>4</sub> requires C, 49.7; H, 5.0; N, 7.0%); CMR(CDCl<sub>3</sub>):  $\delta$  62.0 (2  $\times$  C-6'), 68.0 (C-4'), 68.5 (C-4'), 70.5 (C-2'), 71.0 (C-2'), 77.05 (C-5'), 78.0 (C-5'), 88.5 (2  $\times$  C-1'), 107.0 (C-3a), 129.5 (C-3), 146.4 (C-6) and 157.5 (C-4 and C-7a).

**Fraction C**—It crystallized from ethanol giving 1,5-dihydro-1-(2,3,4,6-tetra-O-acetyl- $\alpha$ -D-glucopyranosyl)-4-*H*-pyrazolo[3,4-*d*]pyrimidin-4-one (VIIa) yield 0.6 g, m.p. 222-23° (Found: C, 48.6; H, 4.7; N, 11.0.  $C_{19}H_{22}O_{10}N_4$  requires C, 48.9; H, 4.7; N, 12.0%); CMR( $CDCl_3$ ):  $\delta$  62.0 (C-6'), 68.0 (C-4'), 69.5 (C-2'), 74.0 (C-5'), 75.0 (C-3'), 82.5 (C-1'), 107.0 (C-3a), 136.5 (C-3), 147.5 (C-6), 154.0 (C-7a), 159.0 (C-4).

**Fraction D**—It crystallized from ethanol giving 2,5-dihydro-2-(2,3,4,6-tetra-O-acetyl- $\beta$ -D-glucopyranosyl)-4-*H*-pyrazolo[3,4-*d*]pyrimidin-4-one (IXa), yield 300 mg, m.p. 285-87° (Found: C, 47.9; H, 4.7; N, 12.4.  $C_{19}H_{22}O_{10}N_4$  requires C, 48.9; H, 4.7; N, 12.0%); CMR( $CDCl_3$ ):  $\delta$  62.5 (C-6'), 68.5 (C-4'), 71.0 (C-2'), 72.0 (C-5'), 73.0 (C-3'), 87.0 (C-1'), 108.0 (C-3a), 129.2 (C-3), 147.5 (C-6) and 158.0 (C-4 and C-7a).

**Fraction E**—It crystallized from ethanol giving 1,5-dihydro-5-(2,3,4,6-tetra-O-acetyl- $\beta$ -D-glucopyranosyl)-4-*H*-pyrazolo[3,4-*d*]pyrimidin-4-one (Xa), yield 270 mg, m.p. 124-25° (Found: C, 48.0; H, 4.7; N, 12.0.  $C_{19}H_{22}O_{10}N_4$  requires C, 48.9; H, 4.7; N, 12.0%).

**1,5-Dihydro-1,5-bis( $\alpha$ -D-glucopyranosyl)-4-*H*-pyrazolo[3,4-*d*]pyrimidin-4-one (VIb)**

A solution of VIa (870 mg) in 100 ml of 0.07*N* methanolic methoxide was stirred at room temperature for 4 hr and subsequently deionized by stirring with a strongly acidic ion exchange resin (5g. DWX-50 Fluka). Removal of resin by filtration, washing with methanol and distillation under reduced pressure gave a residue which crystallized from methanol to give VIb, yield 450 mg, m.p. 185-86° (Found: C, 43.9; H, 5.1; N, 12.4.  $C_{17}H_{24}O_{11}N_4$  requires C, 44.3; H, 5.2; N, 12.7%).

**2,5-Dihydro-2,5-bis-( $\beta$ -D-glucopyranosyl)-4-*H*-pyrazolo[3,4-*d*]pyrimidin-4-one (VIIb)**

It was obtained from VIIa (400 mg), yield 206 mg, amorphous, m.p. 218-20° (Found: C, 44.1; H, 5.3; N, 11.9.  $C_{17}H_{24}O_{11}N_4$  requires C, 44.3; H, 5.2; N, 12.2%).

**1,5-Dihydro-1-( $\alpha$ -D-glucopyranosyl)-4-*H*-pyrazolo[3,4-*d*]pyrimidin-4-one (VIIIb)**

It was obtained from VIIIa (400 mg), yield 220

mg, m.p. 202-3° (Found: C, 44.4; H, 4.6; N, 18.7.  $C_{11}H_{14}O_6N_4$  requires C, 44.3; H, 4.7; N, 18.8%).

**2,5-Dihydro-2-( $\beta$ -D-glucopyranosyl)-4-*H*-pyrazolo[3,4-*d*]pyrimidin-4-one (IXb)**

It was obtained from IXa (180 mg), yield 70 mg, white solid, m.p. 292-95° (Found: C, 44.4; H, 4.7; N, 18.6.  $C_{11}H_{14}O_6N_4$  requires C, 44.3; H, 4.7; N, 18.8%).

**1,5-Dihydro-5-( $\beta$ -D-glucopyranosyl)-4-*H*-pyrazolo[3,4-*d*]pyrimidin-4-one (Xb)**

It was obtained from Xa (200 mg), yield 82 mg, m.p. 97-98° (Found: C, 44.2; H, 4.6; N, 18.6.  $C_{11}H_{14}O_6N_4$  requires C, 44.3; H, 4.7; N, 18.8%).

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## Studies in Potential Filaricides: Part 21—Resolution & Antifilarial Activity of Optical Antipodes of 3-Ethyl-8-methyl-1, 3,8-triazabicyclo[4.4.0]decan-2-one†

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The resolution of ( $\pm$ )-3-ethyl-8-methyl-1,3,8-triazabicyclo[4.4.0]decan-2-one (**3**) using di-*p*-toluoyl-*d*-tartaric acid is described. Both the (+) and (–) enantiomers have been tested for their antifilarial activity against *Luomosoides carini* infection in cotton rats. Though the laevo and dextro isomers of **3**, have almost similar activity, the laevo isomer suppresses the microfilariaemia for a longer duration.

Although introduced in 1948, diethylcarbamazine (DEC, **1**) is still in use as one of drugs for the treatment and control of lymphatic filariasis<sup>1</sup>. The mode of action of DEC still remains a matter of much debate and speculation despite considerable work done in this direction<sup>2</sup>. It has been suggested that DEC modifies the surface layer of the microfilariae thus exposing them to immunological cell-mediated lysis; this mechanism is antibody-dependent<sup>3</sup>. Recently it has been shown that the killing effect of DEC is mediated by blood platelets, with additional triggering of a filarial excretory antigen which is antibody-dependent, and involves participation of free radicals<sup>4</sup>.

The involvement of any receptors, if any, in this cascade of DEC action is not known. One way of obtaining insight into the involvement of receptors in any biological response is to find out if their action is stereospecific. DEC has no asymmetric centre and can not, therefore, provide any information on this point. However, centperazine (CP, **3**), a promising filaricide

discovered in this laboratory some years ago<sup>5,6</sup> has an asymmetric centre and its enantiomers could provide useful insight into the involvement of specific receptors and any stereoselectivity therein. The racemate of CP, was therefore, resolved and both the optical antipodes were evaluated for their antifilarial activity.

Resolution of racemate of CP (**3**), using acids such as camphor-10-sulphonic acid, *d*-tartaric acid and di-*p*-toluoyl-*d*-tartaric acid failed to yield any crystalline salt. The penultimate intermediate of CP, 3-ethyl-1,3,8-triazabicyclo[4.4.0]decan-2-one (**2**), however gave a crystalline salt with di-*p*-toluoyl-*d*-tartaric acid from which the two enantiomers could be separated by fractional solubility. The free amines were liberated on a basic alumina column and the resulting (+) and (–) isomers of **2** were subjected to Clark-Eshweiler methylation to form the corresponding enantiomers of CP.

### Biological activity

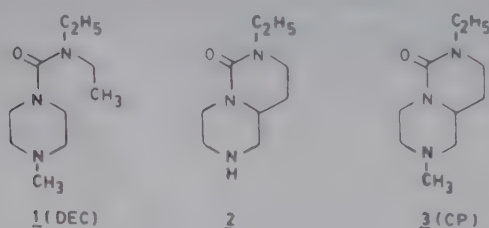
The (+) and (–) enantiomers were tested against experimental filarial infection of *Litomosoides carinii* in cotton rats<sup>7</sup> using racemic CP for comparison. It was found that, within experimental limits, the enantiomers of CP and the racemic compound at a dose of 3 mg/kg, i.p.  $\times$  5 days and 1.5 mg/kg, i.p.  $\times$  5 days, except microfilariaemia remained suppressed upto day 42 and 36 in the case of (–) enantiomer and upto day 36 and 28 in the case of (+) enantiomer, at the active doses respectively both had practically the same order of activity (Table 1).

The lack of stereoselectivity in the action of CP would indicate that the antifilarial action of these compounds may not involve specific receptors but may act in a nonspecific manner on some components of the immune system of the microfilariae.

Melting points were taken in a sulphuric acid bath and are uncorrected. The structures of the compounds were checked by IR and PMR spectra and their purity was checked on silica gel G plates using iodine as visualising agent. The optical rotation was recorded on Carl Zeiss (Germany) polarimeter.

### Resolution of ( $\pm$ )-3-ethyl-1,3,8-triazabicyclo[4.4.0]decan-2-one (**2**)

A solution of **2** (2.6 g, 0.014 mol) in dry acetone (20 ml) was mixed with a solution of di-*p*-toluoyl-*d*-tartaric acid (4.62 g, 0.014 mol) in dry acetone (30 ml). The mixture was warmed for 1 min and left at room temperature overnight. The resulting solid was filtered and washed with dry acetone ( $2 \times 10$  ml), yield 3



†CDRI Communication No. 4111.

Table 1—Comparative Antifilarial Efficacy of CP and Its (+)- and (-)-Enantiomers

Drug	Dose mg/kg, i.p. × 5 days	No. of animals used	Reduction of microfilariae on day(%)	Persistence of microfilaricidal effect (in days)
CP(racemic)	1	5	70-73	21
CP(-)-enantiomer	3	5	100	42
	1.5	5	100	36
CP(+)-enantiomer	3	5	98.2	36
	1.5	5	98.6	28

g (83%), m.p. 182-84°,  $[\alpha]_D -91.3^\circ$  (1% in MeOH) (Found: C, 61.3; H, 6.0; N, 7.5.  $C_{29}H_{35}N_3O_9$  requires C, 61.2; H, 6.2; N, 7.4%).

The mother liquor was concentrated to get a thick syrup which could not be crystallised, yield 3.1 g (85.8%),  $[\alpha]_D -27^\circ$  (1% in MeOH).

The solid, m.p. 182-84°, was dissolved in 5% methanol in ethyl acetate and then passed through a basic alumina column to afford (-)-**2** as a thick oil, yield 0.9g (69%),  $[\alpha]_D -11^\circ$  (1% in MeOH).

In a similar manner the free base, (+)-**2** was obtained from the syrupy salt, yield 0.95 g (73%),  $[\alpha]_D +12^\circ$  (1% in MeOH).

**Methylation of (+)- and (-)-2: Formation of (+)-3 and (-)-3**

To a mixture of (-)-**2** (1.6 g, 0.008 mol) and formic acid (5 ml) was added dropwise 37% formaldehyde (6 ml) and then the reaction mixture was heated gently at 80° for 6 hr. Solvent was removed from the reaction mixture, the residue treated with 5% potassium hydroxide in the cold and the product worked-up in usual manner to get (-)-3-ethyl-8-methyl-1,3,8-triazabicyclo[4.4.0]decan-2-one (**3**), yield 1.2 g

(70%),  $[\alpha]_D -10^\circ$  (1% in MeOH) (Found: C, 60.8; H, 9.5; N, 21.0.  $C_{10}H_{19}N_3O$  requires C, 60.9; H, 9.6; N, 21.3%).

In a similar way, (+)-3-ethyl-8-methyl-1,3,8-triazabicyclo[4.4.0]decan-2-one (**3**) was prepared by treating (+)-**2** (1.2 g, 0.006 mol) with formic acid (4 ml) and formaldehyde (6 ml), yield 1 g (77%),  $[\alpha]_D +10^\circ$  (1% MeOH).

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## *o*-Aminophenyl Alkyl/Aralkyl Ketones & Their Derivatives: Part V — An Efficient Synthetic Route to Some Biologically Active 4-Substituted Quinazolines †

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4-Substituted quinazolines (II) have been prepared by the action of formamide on *o*-aminophenyl alkyl and aralkyl ketones (I) in the presence of borontrifluoride etherate as catalyst, and tested for their inotropic activity.

4-Substituted quinazolines are prepared either by primary synthesis or by dehalogenation of 4-substituted 2-halogenoquinazolines. In the primary synthesis, the pyrimidine ring is built up using formamide or formic acid starting from *o*-aminoaryl ketones often employing drastic conditions like high temperatures. We have recently reported for the first time a primary synthesis of 4-benzyl-6, 7-dimethoxyquinazoline<sup>1</sup> using formic acid and formamide starting from 2-amino-6, 7-dimethoxyphenyl benzyl ketone but 4-benzoyl-6, 7-dimethoxyquinazoline was also isolated as a byproduct in a substantial amount. A similar byproduct was obtained but to a lesser extent during the synthesis of the quinazoline analogue of papaverine<sup>2</sup>. Despite these limitations the formic acid-catalysed synthesis of quinazolines has become the standard practice. Furthermore, another competitive reaction which occurs with formic acid and formamide is the Leuckart reaction involving reduction of a ketonic function to a primary amine. A literature survey indicates that no other catalyst has been used in quinazoline synthesis. In the present investigation borontrifluoride etherate has been used as a catalyst in excess formamide for the synthesis of 4-substituted quinazolines (II). This variation gave good yields and clean products and in the case of 4-benzylquinazoline the

formation of the byproduct was almost eliminated. The physical data of II are given in Table I.

The structural assignments of II were on elemental analyses and spectral data (PMR and mass).

All the starting *o*-aminoaryl ketones were prepared by literature methods except the starting materials Ig and Ib which have been reported by us recently<sup>1,2</sup>.

The cardio-stimulant activity reported for quinazoline derivatives<sup>6,10</sup> prompted us to test some of the synthesised compounds. The testing procedure has been described in an earlier paper<sup>11</sup>; briefly guinea pig paired atria were mounted in McEwen's solution at 37°C for isometric recording. The rate and force of beating were displayed on a Device M2 recorder. Cumulative concentration curves were determined over the concentration range 10<sup>-6</sup> to 10<sup>-4</sup> M. There was a fairly rapid onset of a positive inotropic effect (increased strength of beating) with 5 × 10<sup>-5</sup> M solutions up to 50% of the effect of isoprenaline in the case of 6-chloro-4-phenylquinazoline. There was no significant increase in chronotropic activity at this dose. However, at 10<sup>-4</sup> M concentration a toxic cardiac depressant action ensued. The other compounds tested were less potent but still cardio-toxic. This action resembles that of papaverine and some novel isoquinolines that we have studied earlier<sup>10</sup>. These levels of activity do not warrant further investigation of the compounds as inotropic agents.

### General synthesis

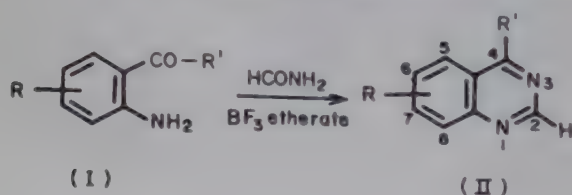
To the *o*-amino ketone (I, Ig) was added formamide (20 ml) containing 2 drops of borontrifluoride etherate-

Table I—Physical Data of 4-Substituted Quinazolines

Compd	R	R'	Yield (%) <sup>*</sup>	b.p./m.p. °C	Inotropic activity †
IIa	H	Methyl	55	85/Imm	—
IIb	6, 7-Dimethoxy	Methyl	48	150-52 <sup>4</sup>	+
IIc	6, 7-Dimethoxy	Ethyl	55	149-50 <sup>5</sup>	+
IId	6, 7-Dimethoxy	Phenyl	60	178 <sup>6</sup>	+
Ile	6-Chloro	Phenyl	83	136-38 <sup>7</sup>	++
IIf	6-Nitro	Phenyl	61	135-37 <sup>8</sup>	+
Ilg	6, 7-Dimethoxy	Benzyl	40	133-34 <sup>1</sup>	—
IIh	6, 7-Dimethoxy	3, 4-Dimethoxy benzyl	45	178 <sup>9</sup>	—

\*The yields reported are for recrystallised pure material. We unable to repeat Palazzo's work which claimed quantitative yields (purity not stated) from reactions using only formic acid and formamide<sup>9</sup>.

†-nil, + slight, ++significant



te. The mixture was heated in an oil-bath at 130-135° for 2 hr when TLC (25% ethyl acetate in benzene) showed the disappearance of the starting material. The mixture was extracted with benzene (3 × 25 ml), and the extract dried over anhyd. sodium sulphate, solvent removed under reduced pressure and the solid residue crystallised from benzene-pet. ether or acetone-pet. ether. Liquid products were distilled.

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## Mass Spectral Fragmentations & Gas Phase Reactions of *t*-Butyl Peresters<sup>†</sup>

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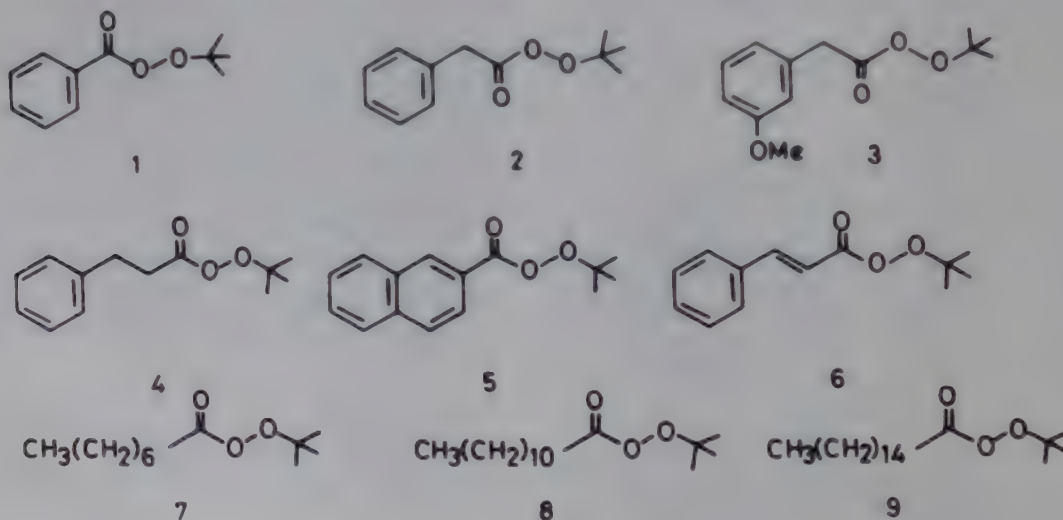
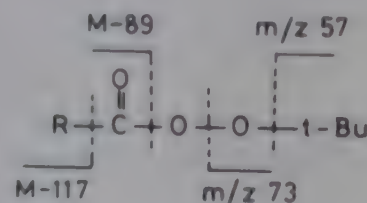
The mass spectral behaviour of a few aliphatic and aromatic peresters has been studied under electron impact (EI) and chemical ionization (CI) conditions. Under EI, fragmentation of the molecules occurs mainly by C-C cleavage at either side of the carbonyl group. The  $C_4H_9O^+$  ion generated by the attack of the CI reagent on the sample molecule adds on to the molecule leading to  $(M+73)^+$  ion in the CI ( $i$ -C<sub>4</sub>H<sub>10</sub>) spectra while with the more basic reagent, NH<sub>3</sub>, clustering of the molecule around NH<sub>4</sub><sup>+</sup> ion is the predominant pathway for ion formation.

Mass spectrometry, particularly GC/MS, has been used for the characterisation of organic peroxides<sup>1-6</sup>. Krull and Mandelbaum<sup>7</sup> have studied the electron impact induced fragmentation of *t*-butyl peresters of a few mono and dicarboxylic acids. Since there appears to be no report on the behaviour of *t*-butyl peresters under chemical ionization conditions, we undertook a comparative study of the EI and CI spectra of the peresters 1-9. The results are reported in this note.

The required peresters (1-9) were prepared by the reaction of the corresponding acid chlorides with *t*-butyl hydroperoxide<sup>8</sup>. To a cooled (ice-bath) stirred solution of the acid chloride (0.016

mol) and *t*-butyl hydroperoxide (0.02 mol) in hexane was added pyridine (0.02 mol) dropwise while the temperature was maintained below 10°. The reaction mixture was stirred for an additional 7 hr at room temperature before work up. The peresters obtained were characterised by their IR and PMR spectral data. The EI and CI spectra were recorded on a Jeol D-300 mass spectrometer under the following ion source conditions: electron energy, 70 eV (EI) and 200 eV (CI); emission current, 100  $\mu$ A (EI) and 300  $\mu$ A (CI) and temperature, 150°C. The source pressure was  $2 \times 10^{-5}$  torr under CI conditions. The exact mass measurements were carried out at a resolution of 5000 using the data system. The high voltage scan metastable spectra were recorded on a Jeol 01SG-2 mass spectrometer at 75 eV and 50  $\mu$ A. The samples were introduced through the direct inlet system.

The ion abundances in the 70 eV EI spectra of 1-9 are given in Table 1. Under EI, these molecules undergo facile fragmentation mainly by the rupture of bonds on either side of the carbonyl group. The base peaks in the spectra of 1-6 correspond to either R<sup>+</sup> or RCO<sup>+</sup>. Compounds



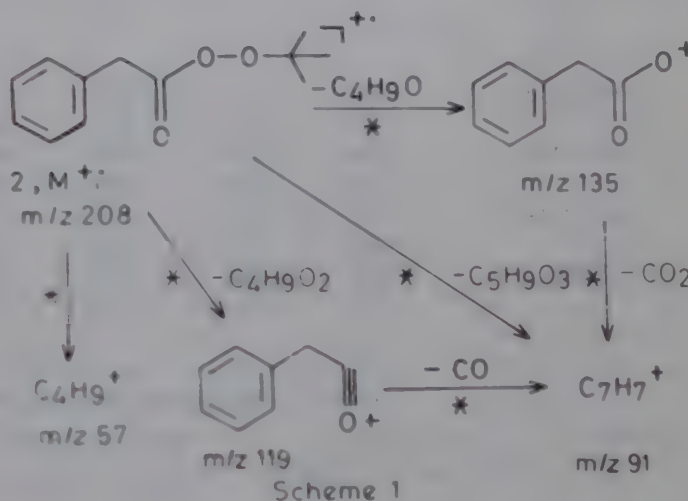
<sup>†</sup>CDRI Communication No. 4012.

Table 1 – Ion Abundances (%) in the EI Spectra of 1-9

Compd	Ions								
	M <sup>+</sup>	(M-73) <sup>+</sup>	(M-89) <sup>+</sup>	(M-117) <sup>+</sup>	m/z 91	M/z 77	m/z 73	m/z 57	m/z 43
1	194(1)	121(0.7)	105(100)	77(17)	–	17	3	7	10
2	208(10)	135(6)	119(15)	91(100)	100	8	11	66	26
3	238(24)	–	149(24)	121(100)	11	5	9	21	14
4	222(0.1)	149(25)	133(33)	105(100)	49	15	14	19	13
5	244(11)	–	155(100)	127(27)	–	–	3	3	5
6	220(3)	–	131(100)	103(31)	5	14	4	12	15
7	216(0.2)	–	127(90)	–	–	–	23	100	31
8	272(0.1)	199(5)	183(94)	–	–	–	62	100	68
9	328(0.1)	255(4)	239(94)	–	–	–	65	100	60

Table 2 – HRMS Data of 2

Ion	Composition	Mass	
		Obsd.	Calc.
M <sup>+</sup>	C <sub>12</sub> H <sub>16</sub> O <sub>3</sub>	208.1088	208.1098
(M-73) <sup>+</sup>	C <sub>8</sub> H <sub>7</sub> O <sub>2</sub>	135.0456	135.0444
(M-89) <sup>+</sup>	C <sub>8</sub> H <sub>7</sub> O	119.0492	119.0495
m/z 91	C <sub>7</sub> H <sub>7</sub>	91.0546	91.0546
m/z 77	C <sub>6</sub> H <sub>5</sub>	77.0391	77.0391
m/z 73	C <sub>4</sub> H <sub>9</sub> O	76.0662	73.0651
m/z 57	C <sub>4</sub> H <sub>9</sub>	57.0697	57.0702



containing aromatic groups not conjugated with the carbonyl function (2-4) give rise to abundant R<sup>+</sup> ions, while all others give abundant RCO<sup>+</sup> ions. Cleavage of the peroxide bond resulting in (M-73)<sup>+</sup> ions is a comparatively minor process except in 4. The various fragmentation pathways of 2, established with the help of high voltage scan metastable spectra and high resolution mass spectral (HRMS) data (Table 2), are shown in Scheme 1. In contrast to this EI behaviour, the known *t*-butyl perester decomposition in the condensed state involves concerted breaking of two bonds leading to the formation of R, *t*-BuO and CO<sub>2</sub><sup>9</sup>. Adam and Tsai<sup>10</sup> have reported similarity between EI induced and photochemical behaviour of peroxy lactones.

The weak or completely absent molecular ion peaks in the EI spectra (Table 1) of these peresters necessitates the use of a soft ionization technique for the unambiguous determination of their molecular weights. If these peresters are stable in the gas phase in the presence of Bronsted acids such as *i*-C<sub>4</sub>H<sub>9</sub><sup>+</sup> and NH<sub>4</sub><sup>+</sup>, their molecular weights can easily be determined from their CI spectra. Table 3 gives the ion abundances in the CI (*i*-C<sub>4</sub>H<sub>10</sub>) and CI (NH<sub>3</sub>) spectra of 1-9. Quite unexpectedly, the most abundant ion in the CI (*i*-C<sub>4</sub>H<sub>10</sub>) spectra of 1-9 appears at *m/z* 73 corresponding to C<sub>4</sub>H<sub>9</sub>O<sup>+</sup> as confirmed by the appro-

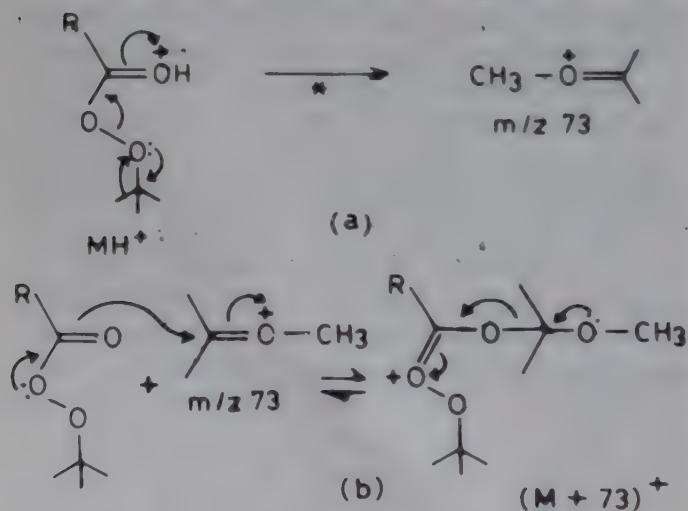
priate isotopic contribution at *m/z* 74 (4.5%). Instead of abundant MH<sup>+</sup> ions, the spectra are dominated by (M+73)<sup>+</sup> ions corresponding to C<sub>4</sub>H<sub>9</sub>O<sup>+</sup> adduct. No evidence (such as metastable peaks) could be obtained for the formation of (M+73)<sup>+</sup> ion from an ion of higher mass such as (2M+H)<sup>+</sup> which gives rise to minor peaks in the spectra of 1-9. It may be noted here that C<sub>4</sub>H<sub>9</sub>O<sup>+</sup> is not a prominent ion in the EI spectra of these compounds except in the aliphatic peresters 7-9. Metastable ion abundances have been used earlier to classify isomeric C<sub>4</sub>H<sub>9</sub>O<sup>+</sup> ions<sup>10</sup>. The C<sub>4</sub>H<sub>9</sub>O<sup>+</sup> ion from the peresters may most probably have the structure (CH<sub>3</sub>)<sub>2</sub>C=OCH<sub>3</sub> as metastable peaks are observed in the spectra of 1-9 at *m/z* 25.5 for the loss of CH<sub>2</sub>O from C<sub>4</sub>H<sub>9</sub>O<sup>+</sup> ion<sup>11</sup>. Under CI (acidic) condition, C<sub>4</sub>H<sub>9</sub>O<sup>+</sup> ions are generated directly from MH<sup>+</sup> ions of the sample molecules as confirmed by the presence of metastable peaks for this process (Scheme 2a, Table 4). Attack of C<sub>4</sub>H<sub>9</sub>O<sup>+</sup> ion can be envisaged to take place on the carbonyl oxygen leading to (M+C<sub>4</sub>H<sub>9</sub>O)<sup>+</sup> ions (Scheme 2b). However, this is a reversible reaction as metastable peaks are observed in the spectra of 1-9 (Table 4) for the transition (M+C<sub>4</sub>H<sub>9</sub>O)<sup>+</sup> → C<sub>4</sub>H<sub>9</sub>O<sup>+</sup> showing

Table 3 – Ion Abundances (%) in the CI Spectra of 1-9

Ion	Compounds								
	1	2	3	4	5	6	7	8	9
CI ( <i>i</i> -C <sub>4</sub> H <sub>10</sub> )									
(2M+H) <sup>+</sup>	389 (5)	417 (1)	477 (1)	445 (1)	489 (23)	441 (6)	433 (2)	545 (4)	657 (0.5)
(M+73) <sup>+</sup>	267 (22)	281 (47)	311 (11)	295 (49)	317 (42)	293 (5)	289 (28)	345 (30)	401 (3)
MH <sup>+</sup>	195 (5)	—	239 (2)	—	245 (41)	221 (18)	—	—	—
(M-98) <sup>+</sup>	105 (7)	—	—	—	155 (26)	13 (9)	127 (3)	183 (5)	239 (1)
<i>m/z</i> 73	100	100	100	100	100	100	100	100	100
<i>m/z</i> 57	54	5	25	28	38	65	21	61	98
<i>m/z</i> 43	22	2	8	7	6	11	8	17	26
CI (NH <sub>3</sub> )									
(3M+NH <sub>4</sub> ) <sup>+</sup>	600 (11)	642 (4)	732 (1)	684 (0.5)	750 (2)	678 (0.5)	666 (7)	—	—
(2M+NH <sub>4</sub> ) <sup>+</sup>	406 (100)	434 (100)	494 (100)	462 (94)	506 (46)	458 (41)	450 (100)	562 (62)	674 (6)
(M+N <sub>2</sub> H <sub>7</sub> ) <sup>+</sup>	229 (3)	243 (12)	273 (12)	257 (6)	279 (13)	255 (11)	251 (4)	307 (3)	—
(MNH <sub>4</sub> ) <sup>+</sup>	212 (35)	226 (93)	256 (100)	240 (100)	262 (100)	238 (100)	234 (89)	290 (100)	346 (100)

Table 4 – Metastable Data of 1-9 from Their CI (*i*-C<sub>4</sub>H<sub>10</sub>) Spectra

Compd	Transition (M+C <sub>4</sub> H <sub>9</sub> O) <sup>+</sup> → C <sub>4</sub> H <sub>9</sub> O <sup>+</sup>	Metastable peak <i>m/z</i>		Compd	Transition MH <sup>+</sup> → C <sub>4</sub> H <sub>9</sub> O <sup>+</sup>	Metastable peak ( <i>m/z</i> )	
		Calc.	Obsd.			Calc.	Obsd.
1	267 → 73	19.95	20.0	1	195 → 73	27.33	27.5
2	281 → 73	18.96	19.0	2	209 → 73	25.49	25.5
3	311 → 73	17.13	17.0	3	239 → 73	22.29	22.3
4	295 → 73	18.06	18.0	4	223 → 73	23.85	24.0
5	317 → 73	16.81	16.9	5	245 → 73	21.75	21.8
6	293 → 73	18.18	18.2	6	221 → 73	24.11	24.0
7	289 → 73	18.44	18.5	7	217 → 73	24.56	24.5
8	345 → 73	15.44	15.5	8	273 → 73	19.52	19.5
9	401 → 73	13.28	13.3	9	329 → 73	16.19	16.3



Scheme 2

thereby that the unimolecular decomposition of the adduct ion involves loss of the neutral sample molecule leading to the regeneration of C<sub>4</sub>H<sub>9</sub>O<sup>+</sup>.

A markedly different behaviour is observed for these compounds when NH<sub>3</sub> is used as the CI reagent. Proton transfer to the sample molecule leading to the generation of C<sub>4</sub>H<sub>9</sub>O<sup>+</sup> is not favoured due to the higher basicity of NH<sub>3</sub>. Clustering of these molecules around NH<sub>4</sub><sup>+</sup> ions is the major reaction under CI (NH<sub>3</sub>) conditions. The cluster ions (3M+NH<sub>4</sub>)<sup>+</sup>, (2M+NH<sub>4</sub>)<sup>+</sup> and (M+N<sub>2</sub>H<sub>7</sub>)<sup>+</sup> have been found to decompose unimolecularly giving rise to (2M+NH<sub>4</sub>)<sup>+</sup>, (M+NH<sub>4</sub>)<sup>+</sup> and (M+NH<sub>4</sub>)<sup>+</sup> ions respectively. The metastable peaks for these processes in the spectrum of 2 appear at *m/z* 293.5 (Calc. 293.4),

117.8 (Calc. 117.7) and 210.1 (Calc. 210.2) respectively for the loss of M from  $(3M + NH_4)^+$  ion at  $m/z$  642 and  $(2M + NH_4)^+$  ion at  $m/z$  434 and  $NH_3$  from  $(M + N_2H_7)^+$  ion at  $m/z$  243.

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## CMR Spectral Studies of Substituted Carbazoles

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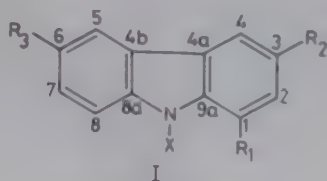
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CMR spectra of five substituted carbazoles have been recorded and analysed. In the case of dibromocarbazole (Ie) and 1-nitrocarbazole (Ic) higher substituent shifts are observed as compared to those in benzenoid compounds.

Carbazole derivatives have been screened by various workers for their biological activities<sup>1-13</sup>. Many of these derivatives and their synthetic analogues possess antiviral<sup>1-3</sup>, bactericidal<sup>4,5</sup> and anti-inflammatory<sup>6-8</sup> activities and some are used as antipresants<sup>9</sup>, fire retardants<sup>10</sup> and CNS active agents<sup>11</sup>. Some of the derivatives are used in the preparation of X-ray sensitive radiographic materials<sup>12</sup> and fire resistant thermoplastic resins<sup>13</sup>. The CMR spectra of some substituted carbazoles have been reported by Ahnoud *et al.*<sup>14</sup>. Prompted by the above biological importance of the substituted carbazoles we have studied the CMR spectra of some carbazoles. The results are reported in this note.

N-Nitrosocarbazole (Ib) on irradiation gave a mixture of 1-nitro-(Ic)- and 2-nitro-(Id)-carbazoles as reported earlier by Sharma *et al.*<sup>15</sup>. The products were isolated by column chromatography. N-Nitrosocarbazole (Ib) was obtained by treating carbazole (Ia) in dioxan with nitrous acid. 3,6-Dibromocarbazole (Ie) was obtained by the light-induced cyclisation of diphenylamine in the presence of N-bromosuccinimide in dichloromethane, and characterised by its PMR and mass spectral data.

The CMR spectra of the carbazole derivatives were recorded in acetone-*d*<sub>6</sub>. The <sup>13</sup>C resonances were assigned by the application of substituent induced shift as well as by OFR spectral analysis.



a, X = R<sub>1</sub> = R<sub>2</sub> = R<sub>3</sub> = H

b, X = -NO; R<sub>1</sub> = R<sub>2</sub> = R<sub>3</sub> = H

c, X = H; R<sub>1</sub> = NO<sub>2</sub>; R<sub>2</sub> = R<sub>3</sub> = H

d, X = R<sub>1</sub> = R<sub>3</sub> = H; R<sub>2</sub> = NO<sub>2</sub>

e, X = R<sub>1</sub> = H; R<sub>2</sub> = R<sub>3</sub> = Br

The magnitude of substituent shift varies according to the nature of the group. The N-nitroso group in Ib has been found to deshield most of the aromatic carbon atoms to varying degrees (cf. Table 1). Introduction of a nitroso group on the nitrogen atom of Ia produces a partial positive charge on ring nitrogen and also on ring carbons C-1, C-3, C-4a, C-4b, C-8a and C-8b due to mesomeric effect thereby providing a rationale for the deshielding of almost all the carbon resonances.

From the calculation it has been shown that there is a deshielding of *ipso*-carbon in all the cases except in the case of bromine as substituent. Literature records instances in benzenoid series where heavy halogens, -C≡H and -C≡N, etc. shield<sup>16</sup> and *ipso*-carbon but the *ortho*-carbons are deshielded. The magnitudes of substituent shifts are rather greater in the case of dibromocarbazole (Ie) and 1-nitrocarbazole (Ic) for rest of the carbon atoms, except the *ipso*-carbon, as compared to the magnitudes in benzenoid series. In the case of Ie the excess substituent effect may be due to additivities of the effects of both the bromine atoms, probably the nitrogen acts as a good conductor of these effects. In the case of 1-nitrocarbazole (Ic) these effects may be attributed to the steric factors/additional ring current which always exhibit deshielding, and thus the additional magnitude of deshielding in the case of Ic for rest of the carbon atoms except the *ipso*-carbon may be rationalised.

One of the striking features of these studies is that the deshielding at the adjacent C-2 carbon in 1-nitrocarbazole (Ic) is greater than in 3-nitrocarbazole (Id). This variation may be attributed to the steric factors or ring current through additional ring formation by hydrogen bonding in the case of Ic.

CMR and PMR spectra were recorded in acetone-*d*<sub>6</sub> on an FT-90 Q (Jeol) NMR spectrometer at 25°C. The chemical shifts were determined by taking acetone-*d*<sub>6</sub> lines as standard (δ 30.3). The time of PD was kept at 10 seconds and 2000 scans were accumulated by CMT system. The multiplicity of the <sup>13</sup>C resonances was established by OFR studies. The CMR spectral data are given in Table 1. The assignments were confirmed by calculation using reported SCS values for aromatic compounds<sup>17</sup>.

### 3,6-Dibromocarbazole (Ie)

To the saturated solution of diphenylamine (1.69 g; 0.01 mol) in dichloromethane (10 ml) was added saturated solution of N-bromosuccinimide (7.12 g;

Table 1— $^{13}\text{C}$  Chemical Shifts (in  $\delta$  ppm) of Substituted Carbazoles (I)  
(Substituent shifts in parenthesis)\*

Carbon atom	Compound				
	Ia	Ib	Ic	Id	Ie
C-1	112.78	115.45 (2.67)	129.32 (16.54)	113.14 (0.36)	119.82 (7.04)
C-2	127.36	129.67 (2.31)	120.25 (-7.11)	122.74 (-4.62)	135.02 (7.66)
C-3	120.78	121.58 (0.80)	122.74 (1.96)	138.83 (18.05)	114.70 (-6.08)
C-4	121.67	121.58 (-0.09)	129.32 (7.65)	118.30 (-3.37)	131.00 (9.33)
C-4a	125.40	128.07 (2.67)	127.27 (1.87)	128.87 (3.47)	131.50 (6.10)
C-4b	125.40	128.07 (2.67)	124.43 (-0.97)	122.92 (-2.48)	131.50 (6.10)
C-5	121.67	121.58 (-0.09)	122.74 (1.07)	122.38 (0.71)	131.00 (9.33)
C-6	120.78	121.58 (0.80)	120.25 (-0.53)	122.03 (1.25)	114.70 (-6.08)
C-7	127.36	129.67 (2.31)	127.27 (-0.09)	128.87 (1.51)	135.02 (7.66)
C-8	112.78	115.45 (2.67)	114.11 (1.33)	112.25 (-0.53)	119.82 (7.04)
C-8a	142.47	143.54 (1.07)	141.76 (-0.71)	138.83 (-3.64)	141.50 (-0.97)
C-9a	142.47	143.54 (1.07)	135.36 (-7.11)	152.29 (9.82)	141.50 (-0.97)

\*Positive substituent shifts indicate deshielding and negative substituent shifts shielding.

0.04 mol) in dichloromethane (175 ml). White needle shaped crystals appeared after irradiating the mixture for 1 hr. The crystals were collected by filtration under suction, thoroughly washed with water and recrystallised from  $\text{CCl}_4$  to give Ie, yield 2.75 g (84.6%), m.p.  $182^\circ$  (Found: C, 44.1; H, 2.2; N, 4.5.  $\text{C}_{12}\text{H}_7\text{Br}_2\text{N}$  requires C, 44.4; H, 2.2; N, 4.3%; IR (KBr): 3370 (-NH), 3050 (=C-H), 1660 (N-H def),  $1320\text{ cm}^{-1}$  (C-N); PMR<sup>1</sup>(acetone- $d_6$ ):  $\delta$  7.80 (2H, *d*,  $J=3\text{ Hz}$ , H-4 and H-5), 7.48 (2H, *dd*,  $J=3$  and  $9\text{ Hz}$ , H-2 and H-7), 7.14 (2H, *d*,  $J=9\text{ Hz}$ , H-1 and H-8), 6.76 (1H, *bs*, NH);  $\text{M}^+$  323, 325 and 327.

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## BOOK REVIEWS

**Organic Photochemistry** by J M Coxon and B Halton (Cambridge University Press, Cambridge), 1987, pp. viii + 243.

Photochemical reactions are involved in life sustaining processes like photosynthesis, vision, vitamin-D synthesis etc. in nature. Although large scale use of photochemical reactions are not many, photochlorination and photooxidation are two examples of technological applications. With the advent of lasers as high energy source for specific wavelength irradiation there is bright hope for production of low volume high technology products in the field of medicine, agriculture, electronics, and nuclear field.

There are not many textbooks on this subject and much of the work is described in specialised publications. The second edition of Organic Photochemistry by J M Coxon and B Halton is an introductory textbook filling this gap. The photophysical phenomena are dealt with briefly in the first chapter. In this book reactions are classified as inter- and intra-molecular types, a departure from the general practice of classification based on chromophore. Differences in the mechanism of pericyclic reactions in ground and excited states are highlighted with a detailed discussion on the application of Woodward-Hoffmann theory of conservation of orbital symmetry, the Mobius and Huckel concepts of stable transition state and Frontier Orbital Theory. The molecular transformations by photochemical means described in this book will certainly induce organic chemists to adapt and exploit these in organic synthesis.

Each chapter gives useful citation to reviews, advanced series, specialized texts and other works of reference from recent literature. This concisely written and well produced book is eminently readable and admirably suited for post-graduate students and research workers.

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